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► To cite this version:

Hans Clevers, Bart de Strooper, Angelika Eggert, Jan Ellenberg, Xosé Fernández, et al.. The Life-Time initiative: Towards cell-based medicine in Europe. *Nature*, 2020, 587 (7834), pp.377-386. 10.1038/s41586-020-2715-9 . hal-03027059

HAL Id: hal-03027059

<https://hal.science/hal-03027059>

Submitted on 27 Nov 2020

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The LifeTime initiative: Towards cell-based medicine in Europe

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99 **LifeTime aims to understand the onset and progression of complex diseases and their**
100 **response to therapy at single-cell resolution. This mission will be implemented through the**
101 **development and integration of single-cell multi-omics and imaging, artificial intelligence**
102 **and patient-derived experimental disease models during progression from health to**
103 **disease. Analysis of such large molecular and clinical datasets will discover molecular**
104 **mechanisms, create predictive computational models of disease progression, reveal new**
105 **drug targets and therapies. Timely detection and interception of disease embedded in an**
106 **ethical and patient-centered vision will be achieved through interactions across academia,**
107 **hospitals, patient-associations, health data management systems and industry.**

108 While advances in medicine have led to spectacular progress in certain disease areas, most
109 chronic disorders still partially or totally escape cure. This is mainly because diseases are
110 detected too late, and/or the selected therapy is inappropriate for the individual concerned.
111 Both can be remedied by a more complete mechanistic understanding of the molecular and
112 cellular events that precede disease onset or that arise during treatment. More accurate
113 cellular and molecular diagnostics will enable disease interception sufficiently early to prevent
114 irreparable damage. To achieve this interceptive medicine (Fig 1), we need to invest in
115 approaches that provide a detailed understanding of the basis of disease heterogeneity in
116 tissues, with sufficient molecular, cellular and temporal resolution. This will enable the
117 detection of disease-promoting events and identify the disease-initiating cells, pathways and
118 target molecules. We must be able to evaluate treatments by quantifying their effects on
119 pathological target cells on a cell-by-cell basis. This strategy has the potential to impact both
120 diagnosis and treatment, improve health and quality of life dramatically and alleviate the
121 societal burden of human diseases such as cancer, cardiovascular and metabolic disorders,
122 chronic inflammation, infectious diseases, and neurological disorders.

123 The LifeTime Initiative, a pan-European community consisting of over 90 research institutions
124 with the support from 80 companies, several funding agencies and national science
125 academies, proposes a forward-looking Roadmap to transform the detection and treatment
126 of complex diseases. Central to LifeTime's approach is the development and integration of
127 novel technologies, such as single-cell multi-omics and high-content imaging, artificial
128 intelligence (AI) and patient-derived experimental disease models. The development and
129 application of these integrated approaches to both experimental and clinical workflows is
130 expected to directly benefit patients. For example, appropriate single-cell based biomarkers
131 will precociously alert physicians that a cell or tissue is entering a disease trajectory.
132 Understanding disease heterogeneity at the cellular level and knowing the molecular
133 aetiology of a disease will allow the systematic identification of drug targets, resistance
134 mechanisms or define therapeutic approaches, based on a given disease's molecular or
135 cellular vulnerability. This strategy differs significantly from the classical approaches in drug
136 discovery ¹. The stratification of patients based on underlying disease mechanisms, assessed
137 *in situ* within single cells, will help physicians select the most appropriate treatment(s) or
138 employ combination therapies that are tailored to the individual. These will be used first to
139 identify cells that are deviating from the healthy trajectory, to steer them away from disease,
140 and later to reduce the threat of relapse (Fig 1). This transformative single-cell data-driven
141 approach has the potential to increase the success rates of clinical trials and to increase the
142 efficiency of novel therapeutic interventions in clinics over the next decade.

143

144

145 **Single-cell based medicine**

146 Cells develop and differentiate along many different specific lineage trajectories forming
147 functionally distinct cell types and states ², which together with their neighbouring cells,
148 underlie normal physiology (Fig 1, blue trajectory). However, even during healthy ageing, cells
149 will accrue many molecular changes that lead to aberrant cellular and tissue states, generating
150 conditions that may progress towards disease. This helps explain why ageing is the largest risk
151 factor for many common diseases ³. Currently, most diseases are only detected once gross
152 physiological symptoms manifest, provoking a visit to the physician or hospital. However, by
153 this time, tissues and organs have often undergone extensive or irreversible changes,
154 precluding reversion to the original healthy state (Fig 1, red trajectory). At this stage, the
155 choice of interventions is typically quite limited, and treatments often involve invasive or
156 aggressive therapies of modest benefit to the patient.

157 Why is our ability to detect diseases earlier and intercept them before they progress so
158 limited? For example, medical imaging technologies, developed over the last 20 years, have
159 enabled the earlier detection of certain pathologies, such as metastatic cancer. Yet, the spatial
160 resolution and sensitivity of these approaches is restricted. More recent technology-driven
161 revolutions provide us with the means to probe a patient's physiology at the level of molecules
162 and cells and place them in the context of tissues. Specifically, we are now able to link genetic
163 variation and phenotypic manifestation to understand the molecular basis of disease ⁴ and
164 create models that recapitulate various aspects of human disease ^{5,6}. Genetic information
165 helps us elucidate the roles of specific pathways in disease progression ⁴. Still, our detection
166 and predictive power is limited, because in most cases our mechanistic understanding of
167 disease is incomplete at the cellular level.

168 Timely detection and successful treatment of disease will depend crucially on our ability to
169 understand and identify when cells deviate from their normal trajectory (Fig 1). The number
170 of potential cellular states associated with disease is vast (Fig 1) and gaps in our knowledge
171 stem from limitations in the approaches currently used to investigate complex disease
172 landscapes. First, only recently have we been able to resolve cellular heterogeneity across
173 space and time. We have an incomplete picture of cell types, cell states, and cell-cell
174 interactions in the body. We need to understand how cells transition between states as they
175 respond to and generate local microenvironments during tissue formation. We must assess
176 cellular heterogeneity and composition changes within tissues during normal physiology and
177 disease progression, for example, the dynamic immune system responses in chronic
178 inflammation or during infection. To address this, we need to understand the molecular
179 mechanisms that define a cell's state, and control its function, fate and trajectory over time.
180 Second, we have been unable to reconstruct a cell's history or predict its future. This is key to
181 understanding how disease states progress or dynamically respond to therapeutic
182 interventions. Overcoming these limitations requires a systematic and longitudinal profiling
183 of samples from many patients to reconstruct and predict the complex molecular networks
184 that drive cellular trajectories over time. Third, computational frameworks for integrating
185 temporal data as well as patient profiles with large cohorts to identify regulatory changes and
186 to dissect the causes and manifestations of disease remain elusive. Current attempts to model
187 human disease have not succeeded in integrating the thousands of molecular phenotypes that
188 are acquired from patients. Finally, we are limited by our lack of knowledge of the underlying
189 causes of disease. Any given patient's response to a specific therapy may require testing or
190 modifying cells from the patient in an experimental system, a challenge yet to be routinely
191 implemented.

192 Below, we outline technologies at the heart of LifeTime’s approach and present a roadmap
193 for their implementation with the aim of improving the detection and treatment of diseases.
194 Building on related international initiatives that are paving the way by producing reference
195 maps of healthy tissues in the body, such as the Human Cell Atlas (HCA) ⁷, the NIH Human
196 Biomolecular Atlas Program (HuBMAP) ⁸, and in close collaboration with industry and patients,
197 we foresee the possibility to apply novel technologies to clinical samples, to achieve the
198 necessary molecular and cellular high-resolution view of disease.

199

200 **Technology development and integration**

201 Single-cell technologies, particularly transcriptomics, are generating the first reference cell
202 atlases of healthy tissues and organs, revealing a previously hidden diversity of cell subtypes
203 and functionally distinct cell states ⁷. Application of single-cell approaches to patient’s samples
204 are beginning to provide snap-shots of the changes in cell composition, states and pathways
205 associated with diseases including cancer ⁹⁻¹⁴, chronic inflammatory diseases ^{15,16}, Alzheimer’s
206 disease ¹⁷⁻¹⁹ heart failure ²⁰, and sepsis ²¹. Some studies already provide insight into the basis
207 of early disease detection, by identifying the cells of origin ²², or by showing how a chronic
208 inflammatory environment can lead to tissue remodeling during the evolution of colorectal
209 cancer ^{23,24}. Predicting the future course of a cell requires data from patients that are linked
210 to clinical outcomes. Only then can we identify the cellular parameters that are permissive to
211 a therapeutic response, for example during checkpoint blockade immunotherapy ^{11,25,26},
212 treatment of multiple myeloma ¹⁰, anti-TNF therapy for Crohn’s disease ²⁷, or the evolution of
213 chemo-resistance during treatment of triple-negative breast cancer ²⁸. If we can detect rare
214 drug resistant cells that are present prior to ^{10,28} or that emerge during treatment ²⁹, we can
215 adapt therapeutic regimens and employ combinatorial treatments to improve outcome.

216 Since pathophysiological processes within individual cells can occur on different molecular
217 levels, understanding the underlying mechanisms requires integration of current single-cell
218 approaches, such as RNA-seq, (Fig. 2), with methodologies that provide additional information
219 on chromatin accessibility, DNA methylation, histone modifications, 3D genome organization,
220 and genomic mutations ³⁰⁻³². Future developments in instrumentation promise to couple
221 these genomics approaches with single-cell proteomes, lipidomes, and metabolomes, adding
222 crucial insight into different cellular states and their roles in health and disease. In addition to
223 specific cell subtypes and the role of cellular heterogeneity, it is crucial to investigate the
224 surrounding tissue context and organ environment. This is becoming possible through the
225 development of new spatial multi-omics approaches, particularly spatial transcriptomics, that
226 include information on the location of diseased cells with respect to each other as an integral
227 part of the data ³³⁻³⁸. Novel advanced imaging approaches also now enable systematic spatial
228 mapping of molecular components, *in situ*, within cells and cells within tissues ^{34,39-43}. The
229 cellular context with respect to different immune and stromal cell types, extracellular
230 components and signaling molecules that contribute to disease progression will help identify
231 the roles of specific cell types and interactions in diseases ^{38,44-46}. The implementation of cell
232 lineage tracing approaches ⁴⁷, which link cellular genealogies with phenotypic information of
233 the same cells, may help us understand how populations of cells develop dynamically to form
234 the specific architecture of a healthy or a diseased tissue.

235 The LifeTime initiative proposes to develop necessary single-cell methodologies and end-to-
236 end pipelines (Fig 2), that will be integrated into robust, standardized multi-omics and imaging
237 approaches, and scaled to be able to profile and map hundreds of thousands of patients’ cells.

238 This will be done in close collaboration with health care providers, to enable an in-depth
239 analysis of longitudinal human samples obtained from patients and cohorts (Fig 3). Handling
240 these large molecular datasets will require sophisticated and distributed computational and
241 bioinformatics infrastructures, (see Implementation and Infrastructure), as well as the
242 development of tools to integrate and ensure interoperability of different data types,
243 including single-cell multi-omics, medical information and electronic health records. This will
244 allow the development of advanced personalized models of disease. To be able to implement
245 routine longitudinal sampling of patients, we will need to develop methods for sampling small
246 biopsies, including liquid biopsies that will detect individual cells or cell-free DNA released
247 from pathological cells before and during therapy ⁴⁸. Multi-dimensional descriptors of cell
248 states from patients taken from different stages of disease or therapy will be used to derive
249 new biomarker sets or enhance current panels. Collaboration with ongoing atlas projects,
250 industrial partners and regulatory authorities, will be key for benchmarking and deriving the
251 new standards that will enable us to deploy these new methods in the clinic. This will hopefully
252 achieve earlier disease detection and guide the appropriate selection of drug targets and
253 therapies (Fig 3).

254 Unlocking the potential of unprecedented amounts of integrated digital information requires
255 AI, in particular machine learning approaches that can identify meaningful molecular patterns
256 in the datasets ^{49,50}. Although such approaches have proven very useful when applied to
257 medical imaging data and have enabled the identification of subtle disease-associated
258 changes ⁵¹, medical imaging cannot capture the full complexity of human physiology nor the
259 status of the disease at the single-cell level. Machine learning will be key to fully exploiting the
260 high-quality, petabyte scale data generated by LifeTime, by delivering true integration and
261 systems that can "learn" and reason upon biology to identify disease-associated changes and
262 patterns ^{49,52}. High-content imaging, together with gene expression profiling, chromatin
263 states, protein and metabolic parameters will contribute to the stratification of disease
264 phenotypes. Machine learning and advanced modelling approaches will be used to integrate
265 and analyze the different layers of cellular activity, and generate multi-scale and causal models
266 that will allow us to infer regulatory networks and predict present and future disease
267 phenotypes at the cellular level ^{49,52,53} (Fig 2).

268 The deep integration of machine learning technologies with spatial multi-omics and imaging
269 technologies and data has the potential to usher in a new age of digital pathology to aid the
270 decision-making process of physicians (Fig 3). By considering not only anatomical,
271 physiological and morphological aspects, but also multidimensional molecular and cellular
272 data, it will be possible to provide a more granular representation of a patient's disease state
273 to complement the pathologist's slides and bulk measurements in tissues (e.g. mRNA,
274 metabolites). We envision as the final goal the incorporation of new AI-based decision-aiding
275 systems that will integrate and interpret available molecular, cellular, individual disease
276 trajectory and imaging information. Importantly, interpretable and accountable AI systems
277 will also provide the basis for the predictive models and clinical recommendations. Integration
278 of cellular information should lead to a more precise description of a patient's molecular and
279 physiological history, and will guide early detection, allow predictive prognosis, and guide
280 recommendations for therapeutic interventions to deliver more precise and effective
281 treatments (Fig 3).

282 Understanding the cellular origin and aetiology of disease from a patient-centered perspective
283 requires systems that faithfully recapitulate key aspects of a patient's pathophysiology, and
284 render them experimentally tractable. Organoids are an emerging experimental system that

285 allow modelling aspects of organ development, regeneration and pathophysiology ^{5,6,54} (Fig
286 2). Derived from adult or pluripotent human stem cells, organoids can capture individual
287 features that are unique to each patient and can be interrogated molecularly in space and
288 time. Importantly, by comparing organoid models from diseased and healthy individuals,
289 unique disease features can be extracted even without knowing the specific genetic cause of
290 the disease. Therefore, organoid models offer a unique tool for achieving some of the main
291 goals of LifeTime, especially in cases where repeated access to patient tissues is limited or
292 impossible, for instance for neurological disorders.

293 Organoids have received great attention, both in the scientific and wider community as a tool
294 for modelling disease ⁵⁵⁻⁵⁷. Yet they still require significant development to harness their full
295 potential (Fig. 2). While current organoid models contain multiple organ cell types, more
296 complex extracellular matrices and chemical gradients are required to capture the full degree
297 of cellular heterogeneity as well as tissue-specific structural and metabolic conditions ⁵⁸. The
298 next generation of models will need to incorporate key physiological aspects, such as immune
299 response, vascularization or innervation. Because complex interactions between multiple
300 tissues and organs are involved in many diseases, it will be necessary to develop novel tissue
301 engineering principles that combine multiple organoids in pathophysiologically relevant
302 crosstalk (organoid-on-a-chip). To harness their full translational potential, LifeTime will
303 engage in standardizing, automating and scaling organoid approaches, allowing for systematic
304 derivation, propagation and banking. Such industrialization is also needed for large scale
305 chemical or genetic perturbations (e.g. CRISPR-Cas screens), and for elucidating the genetic
306 basis for disease variability and drug response at population-relevant scales, in both the
307 preclinical and clinical context (Fig 3). The resulting mechanistic dissection enabled by large-
308 scale perturbations will be used to validate corresponding AI models of disease interception
309 and progression. This approach is enabled by iterative rounds of reinforcement learning that
310 continuously improve these models of human disease.

311 In addition to organoids, *in vivo* model systems are necessary to translate the science from
312 bench to humans. A complex biological system is required to study the myriad of host-disease
313 and pathogen interactions associated with complex diseases, such as infectious diseases,
314 cancer or Alzheimer's disease. The use of animal models is important for understanding the
315 very complex temporal relationships that occur in disease such as those involving the
316 vasculature and blood brain barrier, the resident microbiota, the immune system and
317 pathogens as well as neuronal networks in the brain. LifeTime will therefore make use of
318 models in which patient-derived tissues can be integrated into *in vivo* models ⁵⁹⁻⁶³. This
319 initiative is identifying opportunities and challenges for improving existing *in vivo* models, as
320 well as the technological developments needed to improve their clinical relevance and render
321 them suitable for studying dynamics of cellular heterogeneity in space and time.

322 LifeTime, as a community, has the capacity to develop and integrate these technologies, that
323 often require expertise and specialized instrumentation located in distinct laboratories. A
324 coordinated effort will leverage individual expertise and perform the required benchmarking
325 and standardization of technologies, workflows and pipelines. This will also ensure that the
326 data, software and models generated adhere to Findable, Accessible, Interoperable, and
327 Reusable (FAIR) principles ⁶⁴ (see infrastructure below), are available across national borders,
328 and are in full compliance with international legislations such as the General Data Protection
329 Regulation (GDPR) in the EU. Moreover, LifeTime will ensure that technologies, including AI
330 and organoids, will be developed in an ethically responsible way in collaboration with patients,
331 putting the patients at the centre. (see Ethical and Legal Issues).

332 **LifeTime disease Launchpad to identify priorities**

333 The Launchpad mechanism is an innovative platform that allows LifeTime to identify disease
334 areas where the application of these integrated technologies is expected to have direct impact
335 on patient care. Initially, the focus has been on five disease areas that are a significant burden
336 to society: cancer, cardiovascular and metabolic disorders, chronic inflammatory and other
337 autoimmune diseases, infectious diseases, and neurological disorders. Importantly, other
338 disease areas will be continuously monitored. The LifeTime Launchpad has initiated the
339 identification of clinical challenges in each disease area, and is evaluating specific diseases,
340 groups of diseases or pathomechanisms on which research needs to focus. The criteria used
341 to evaluate the proposed applications include: societal impact (including incidence and
342 prevalence, disease severity, economic impact and the pressing need for new and more
343 efficient clinical treatments and early detection), evidence for cellular heterogeneity that
344 limits current clinical avenues, availability of samples from biobanks, relevant preclinical
345 models, existence of patient cohorts including those enabling longitudinal studies, clinical
346 feasibility and ethical considerations, as well as alignment with national and EU funding
347 priorities. A working group will ensure that sex and gender aspects are fully incorporated
348 during the process.

349 The LifeTime Launchpad is currently identifying the impact that the initiative can have in each
350 disease area, to determine common and disease-specific challenges in the early detection of
351 disease onset, or in tailoring therapeutic selection for each patient. For example, in
352 neurodevelopmental and neurodegenerative diseases, a major challenge is to understand the
353 molecular and cellular basis for disease onset and progression, as this would enable the
354 stratification of patients based on molecular subtypes, and would enable the redesigning of
355 clinical trials based on disease mechanism subgroups. Great potential exists for developing
356 new preclinical models based on patient-derived cells, to understand disease processes and
357 mechanisms, as well as for testing new drugs and therapies. A similar scenario exists for
358 understanding the cellular and molecular mechanisms that lead to sepsis and heart failure.
359 The role of cellular heterogeneity in the pathology of cancer and chronic inflammatory
360 diseases is only beginning to be revealed ^{65,66}. There is an urgent need to explore and
361 understand how this relates to the predicted course of disease such as dissemination,
362 response of a patient to one of the numerous available therapies and the development of
363 therapy resistance.

364 The Launchpad process is also identifying themes that span disease areas and will benefit from
365 coordinated research. For example, inflammation-based mechanisms and the role of
366 metabolism in disease, as well as links between infection/inflammation and cardiovascular
367 diseases, cancer or neurological disorders.

368

369 **Implementation and Infrastructure**

370 The scale of the data that will be generated and analyzed, the cross-disciplinary and
371 international structure combined with the ambition of LifeTime to pioneer novel analytics
372 using AI, places LifeTime in an excellent position to shape the next generation of European
373 medical and biological data computational infrastructure. This will require close interaction
374 with and evolution of the established European infrastructure (Fig 4), such as the European
375 Open Science Cloud (EOSC) and high-performance computing infrastructures through
376 EuroHPC. LifeTime will also interact with related European Research Infrastructures including

377 ELIXIR, Euro-Bioimaging, EU-OPENSURE, ECRIN, EATRIS and BBMRI and their cluster
378 initiative EOSC-Life to create added value and to avoid duplication of efforts in strategies and
379 tools for sharing and accessing data, development and application of standards. As medicine
380 is inherently decentralized, LifeTime will also contribute to connecting EU medical systems
381 and large centralized European data infrastructures.

382 To implement LifeTime successfully, fragmentation of research across borders, disciplines and
383 timeframes needs to be overcome. LifeTime data generation and technology development
384 will be harmonized across expert groups and centres, allowing results to be quickly picked up
385 and applied in clinics. This relies on a coordinated approach that integrates the
386 multidisciplinary expertise of single-cell technologies, data science, AI/machine learning, and
387 organoids across Europe. It must also engage clinicians and patients to achieve major medical
388 impact. The LifeTime strategy envisions a multidisciplinary network of LifeTime Centres (Fig 4)
389 with different complementary thematic clusters across Europe, each working in close
390 association with hospitals. These connected, but geographically distributed, flexible
391 innovation nodes will share resources, gather the necessary critical mass for global
392 competitiveness, and be open for collaboration with the entire scientific community.
393 Importantly, LifeTime Centres should deliver a number of key functions:

- 394 • Serve as platforms for the development and advancement of breakthrough
395 technologies for single-cell research in omics and imaging, AI/machine learning and
396 experimental/computational disease models.
- 397 • Closely and actively collaborate with patients, clinicians, hospitals and healthcare
398 systems, in some cases with a specific disease focus.
- 399 • Set standards in data generation, standardization and management implementing
400 FAIR principles.
- 401 • Set standards in ELSI programs (ethical, legal and societal issues) by working together
402 in multidisciplinary teams aimed at responsible research and innovation.
- 403 • Offer opportunities to collaborate, test and benchmark new methodologies and
404 analysis methods e.g. in adaptive experimental design.
- 405 • Offer unique opportunities to industry to translate recent knowledge and novel
406 technologies from the laboratory to the market.
- 407 • Provide an early access programme to new technologies developed by companies.
- 408 • Function as open, interconnected education hubs, delivering training in the new
409 technologies to researchers, scientific personnel and clinicians, as well as provide
410 engagement activities for patients and citizens.

411 A federated LifeTime data and computational network building on cloud technologies will
412 provide the necessary capacities to enable federated analytics across the LifeTime centres and
413 will provide a technical and legal framework for integrating core information structures, multi-
414 omics assays, imaging, AI/machine learning technologies and health records (Fig 4). A joint
415 Data Coordination Centre following a multi-level approach will ensure transparent data access
416 control, compatibility and standardization and allow to establish a quality management
417 programme including interlab quality assessments. Within this Framework LifeTime will also
418 coordinate and pioneer open data sharing and reuse and collaboration, including access
419 models prior to publication of data.

420 To start this cooperative LifeTime Centre network, the initiative can build on first efforts by
421 LifeTime members in a number of European countries, examples are the VIB Single-cell
422 Accelerator Programme in Belgium, Berlin Cell Hospital, the UK's Sanger/EBI/Babraham Single
423 Cell Genomics Centre, or the LifeTime Single-Cell Centre in Poland, to name a few. To avoid
424 duplication and lack of standardisation, the LifeTime Cell Centre network could be coordinated
425 through an entity or framework that optimises coordination and support to achieve the
426 LifeTime vision. Funding for specific research projects that involve one or more LifeTime
427 Centres could come from a portfolio of private and public funding opportunities, both on the
428 national and pan-European level. The network will closely interact with key European efforts
429 and will contribute to EU strategies and programmes.

430

431 **Interaction with industry/innovation framework**

432 Collaborations with the private sector will be key for the successful translation and delivery of
433 technologies, instrumentation, diagnostics and therapies (Fig 4). Currently 80 companies
434 support LifeTime's vision to revolutionize healthcare. These span multiple sectors as well as
435 industrial associations and networks such as the European Federation of Pharmaceutical
436 Industries (EFPIA), which unites major pharmaceutical enterprises, and the Euro-Biolmaging
437 Industry Board (EBIB), which unites major European imaging ventures.

438 Discussions between academic and industry representatives have identified crucial steps for
439 transforming breakthrough discoveries into solutions that will improve the health of European
440 citizens. This includes creating a unifying framework that fosters and streamlines pre-
441 competitive interactions between academia and industry at the interface of computer
442 science, single-cell biology, -omics, imaging, patient-derived disease modelling and precision
443 medicine. A large-scale collaboration platform across Europe should be developed that
444 includes umbrella agreements, regular physical meetings, dual training of early-career
445 scientists in academia and industry, as well as exchange programs. This will enable joint
446 projects between public and private sectors spanning the entire biomedical innovation cycle
447 from discovery research, technology development and implementation in hospitals and the
448 healthcare industry.

449 Cross-sectoral collaborations between small, medium-size and large companies with different
450 development timelines and distinct business models is crucial. These long-term networks will
451 be open to academic institutions, hospitals and technology providers and provide flexible new
452 modes of stimulating innovation. To expedite the identification, and investment in the
453 emerging technologies developed in academic and industry laboratories, successful local
454 initiatives such as the tech watch programs and accelerator schemes (e.g. the VIB Single-cell
455 Accelerator) should be scaled and coordinated at the EU level. LifeTime aims to create a
456 networking/match-making platform for individuals, academic and industry organizations that
457 share the goal to develop and integrate breakthrough technologies and apply them in the
458 clinic to benefit patients. Further measures could foster innovation and entrepreneurship
459 within the LifeTime consortium. For example, a pre-seed, pre-incubator funding scheme based
460 on competitive calls to support start-up or tech transfer ideas.

461 Creating a dedicated European ecosystem is essential since the path to innovation is not linear
462 and includes several feedback loops. To this end, additional key measures such as the
463 development of enabling digital environments, training, promotion of early disease
464 interception with all necessary stakeholders (patients, regulators, payers, etc.) are essential

465 as described in the LifeTime call for action launched in December 2019 endorsed to date by
466 both individuals and organizations ([https://lifetime-fetflagship.eu/index.php/make-eu-](https://lifetime-fetflagship.eu/index.php/make-eu-health-research-count/)
467 [health-research-count/](https://lifetime-fetflagship.eu/index.php/make-eu-health-research-count/)).

468

469 **Ethical and Legal Issues**

470 The implementation of LifeTime’s vision triggers relevant ethical questions from all societal
471 groups directly impacted by the project (patients, clinicians and scientists), and society in
472 general. LifeTime aims to pioneer a real-time or parallel ELSI (ethical, legal and societal issues)
473 program that will predict, identify, monitor and manage the ethical impact of the biomedical
474 innovations that arise from research and technology development, ensuring that
475 implementation follows ethical guidelines. LifeTime’s ELSI program can be used as a testing
476 ground for other international interdisciplinary initiatives (Fig 4). Ethical issues will be
477 identified and managed as early as possible and ensure that ethical and research integrity
478 guidance is implemented throughout the entire research process to stimulate positive effects
479 and mitigate negative ones. Ethics engagement can take different forms, from ad hoc
480 consultation to an embedded ethicist or ethics team that works alongside the research team.
481 LifeTime projects will adopt a prospective ethics mechanism that is more akin to the latter,
482 rather than a retrospective ELSI team in order to be able to steer the development of LifeTime
483 projects in a responsible manner ⁶⁷.

484 LifeTime partners and clinicians have initiated a partnership with specialists in bioethics,
485 public engagement, ethics of technology and lawyers, that resulted in the identification of
486 LifeTime’s ethical and societal priority areas. These include questions related to the
487 derivation, storage and use of organoids, the use of AI, data ownership and management,
488 anonymisation of data, equity of access to such revolutionary medical care, the definition of
489 health and illness, and transparent science communication to society. Initiating a relationship
490 of trust with citizens will include novel modes of communication and engagement, for
491 example through art, gaming or citizen science, to promote individual and critical thinking.

492 With a patient-centred research program as a foundation, compliance with the GDPR is a
493 priority for LifeTime. This is particularly challenging since GDPR implementation, as well as
494 consent form schemes, are not uniform across Europe. LifeTime will therefore establish a
495 team working towards a unified consent procedure to determine: i) who controls the data, ii)
496 who is responsible for the control, and iii) who is liable in case of legal challenge. Moreover,
497 one aspect of LifeTime is its close relationship with industrial partners, which can pose
498 difficulties when obtaining patients’ consent to access data and/or samples. These legal
499 matters are being addressed particularly with respect to data generated from human samples,
500 prioritizing ethically-sound data sharing and data management policies that will ensure the
501 protection of personal data. Our goal is to facilitate the exchange of materials and research
502 data (e.g. through establishing expedited uniformized MTAs), while protecting the patient.

503

504 **Education and Training**

505 To ensure uptake and integration of the LifeTime approaches into common practice, it will
506 require the creation of a LifeTime Academy, which will provide the comprehensive training
507 programs that are necessary to ensure efficient implementation of new technologies and new
508 medical approaches (Fig 4). Importantly, this will be done in an integrative scheme,
509 intersecting the multiple LifeTime disciplines and areas of actions: disruptive technologies

510 applied to medical challenges, technology transfer and innovation, research integrity, data
511 management and stewardship, ethical, integrity, legal and societal issues. The Academy will
512 have an inclusive philosophy to ensure that it can provide training to the wide community,
513 which includes researchers, clinicians, technical operators, managers and staff of technology
514 platforms, as well as administrators, patients and the lay public.

515 Training activities will be conceived and organized by dedicated teams involving specialists
516 with a scientific education. LifeTime Academy envisions the formulation of both short and
517 longer courses over several days and weeks, respectively, providing the trainees with new sets
518 of skills. Additionally, the LifeTime Academy will explore the establishment of Masters and
519 PhD programs, as well as the creation of novel training themes such as “artificial intelligence
520 and medicine”. The LifeTime Academy will therefore engage and inform society, and will train
521 a new generation of highly skilled medical scientists and support staff, in order to foster
522 scientific and medical excellence in an ethical, responsible and inclusive framework.

523

524 **Introduction and acceptance of interceptive medicine**

525 For many medical conditions, early treatment offers the potential to slow or even prevent an
526 individual’s disease from progressing, and is the best situation from which to seek a cure. The
527 concept of interceptive medicine refers to the development of drugs or other medical
528 interventions that work at the earliest time points in the disease process, even before the
529 manifestation of disease symptoms. This requires the availability of appropriate biomarkers.
530 LifeTime aims to introduce interceptive medicine into clinical practice, which will require
531 capacity building in health systems and significant technology deployment in the clinics. The
532 role of a LifeTime Academy for training tomorrow’s physicians, researchers and nurses will be
533 essential, not only in identifying the priorities and needs of the clinical workforce and in
534 educating those involved in technology development, but also developing new professional
535 curricula, for example, in health information counselling.

536 Our ability for early detection of disease may give rise to new concerns among patients and in
537 the healthy population. Many citizens fear that their privacy, security or safety could be at
538 risk. Thus, involvement of patient advocacy groups, public education and promoting critical
539 thinking amongst citizens will be crucial for acceptance and participation in this new way of
540 delivering medicine.

541

542 **Impact on medicine and healthcare.**

543 Medicine and healthcare are rapidly expanding pillars of our economy. EU countries
544 collectively spend more than €1,400 billion per year on healthcare for their 500 million
545 citizens. Given the dimensions and spiraling healthcare costs associated with an ageing
546 population, these numbers will continue to increase unless we can mitigate the damaging
547 effects of ageing. We expect that coupling the current health monitoring with early detection
548 and disease interception, will have a major economic impact. In Europe, 20% of the population
549 will soon be over 65, with an age distribution that will continue to change until 12% are over
550 80 in 2080¹. Given the prevalence and cost of caring for people with degenerative conditions
551 and the increase in chronic lifestyle-induced diseases, the knowledge and technologies
552 developed by LifeTime will allow us to detect them earlier, and avoid their worst

¹ People in the EU – population projections. (2015) <http://ec.europa.eu/eurostat/statistics-explained/index.php/>

553 manifestations. LifeTime would also have an impact in the era of unexpected pandemics such
554 as COVID-19 by rapidly determining the cellular and molecular basis of the disease. This would
555 identify potential therapeutic strategies for patient subgroups as well as starting point for the
556 development of new efficient therapies.

557 It is within LifeTime's vision to work with companies from multiple sectors and healthcare
558 systems, as well as European and national regulatory bodies and patients
559 associations/platforms, to establish new frameworks for robust science-based health policies.
560 These will integrate the newly developed tools and technologies into standard care, and make
561 innovative early detection tools and novel therapies rapidly accessible to patients. The aim is
562 to provide better value to healthcare payers through pricing schemes that include value-based
563 pricing, based on real world data and healthcare economic comparisons.

564 One of healthcare's largest outstanding issues is that many patients do not respond to
565 commonly prescribed treatments. Whereas well-controlled randomised clinical trials provide
566 evidence for statistical utility of a given therapy, in actual practice often many patients must
567 be treated before a single patient will show a measurable benefit. Other patients may not
568 benefit at all or even be harmed⁶⁸ leading to an economic loss that is estimated to be in the
569 hundreds of billions €/year. The variable therapeutic responses originating from the cellular
570 and genetic heterogeneity that exists in cancer and other complex diseases, contributes not
571 only to the failure of treatments, but also to the rising cost of drug development, which is
572 currently estimated at ~€1-2 billion per drug. *In silico* models for disease trajectories
573 generated by LifeTime will enable the integration of personal genetic and lifestyle information
574 into predictive models of disease course. This will allow physicians to determine and
575 implement optimal therapeutic strategies tailored to the individual (precision medicine) with
576 sophisticated timing of disease interception. The knowledge gained will also contribute to a
577 more appropriate selection of patients for clinical trials.

578

579 **Outlook summary**

580 Recent advances in key single-cell technologies, AI and patient-based experimental systems,
581 such as iPSC and organoids, have set the stage for their integration and deployment to address
582 important medical challenges. Patients will benefit from cell based medicine through the
583 earlier detection of diseases at a stage where they can be effectively intercepted. The novel,
584 integrated technologies will enable the selection, monitoring and, if necessary, modification
585 of therapeutic strategies for an individual to improve clinical outcomes based on high-
586 resolution cellular information. Within the next decade, the obtained molecular mechanistic
587 information has the potential to revolutionize drug discovery processes, clinical trial design,
588 and eventually be incorporated into clinician's daily decision-making processes. As the
589 LifeTime community continues to grow and the needs of industry and hospital stakeholders
590 are embraced, this platform will provide unprecedented opportunities to implement single-
591 cell and data-driven medicine to address the growing burden of complex and chronic diseases.

592

593 **Acknowledgements**

594 We would like to acknowledge all participants that have attended and contributed to LifeTime
595 meetings and workshops through many exciting presentations and discussions. LifeTime has
596 received funding from the European Union's Horizon 2020 research and innovation
597 framework programme under Grant agreement 820431.

598

599 **Competing Interests**

600 C.B. is an inventor on several patent applications in genome technology and cofounder of
601 Aelian Biotechnology, a single-cell CRISPR screening company. H.C. is a non-executive board
602 member of Roche Holding, Basel. A.P. holds European and US patents on “Genome
603 Architecture Mapping” (EP 3230465 B1, US 10526639 B2). W.R. is a consultant and
604 shareholder of Cambridge Epigenetix. T.V. is co-inventor on licensed patents
605 WO/2011/157846 (Methods for haplotyping single cells), WO/2014/053664 (High-throughput
606 genotyping by sequencing low amounts of genetic material), WO/2015/028576 (Haplotyping
607 and copy number typing using polymorphic variant allelic frequencies).All other authors
608 declare no competing interests.

609

610

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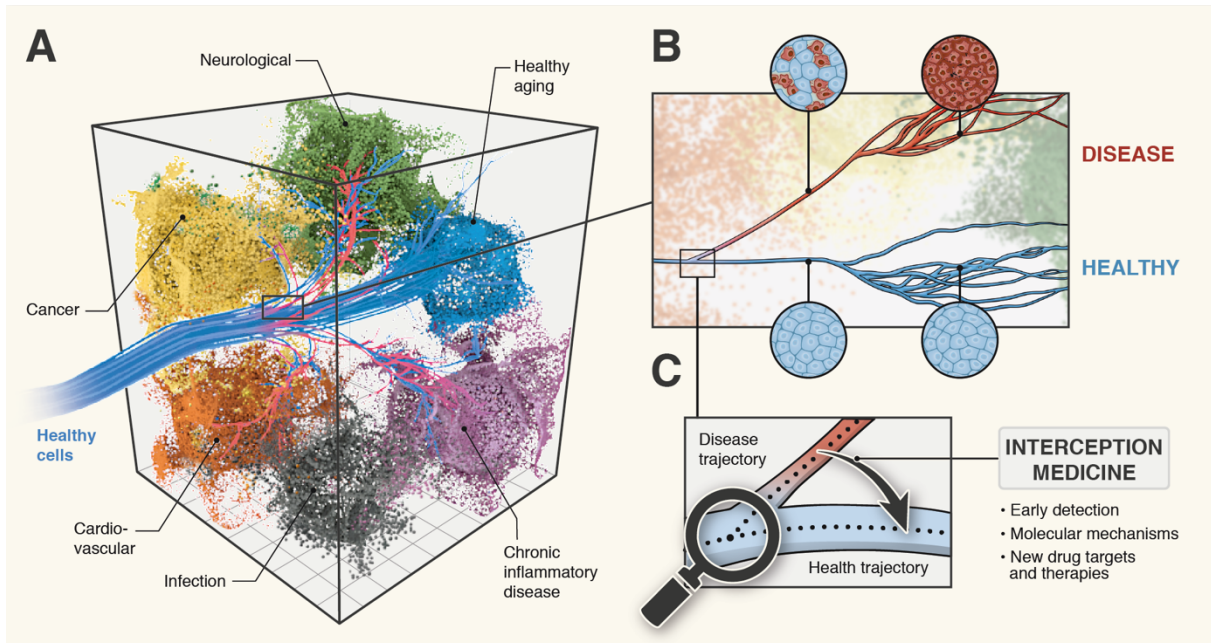
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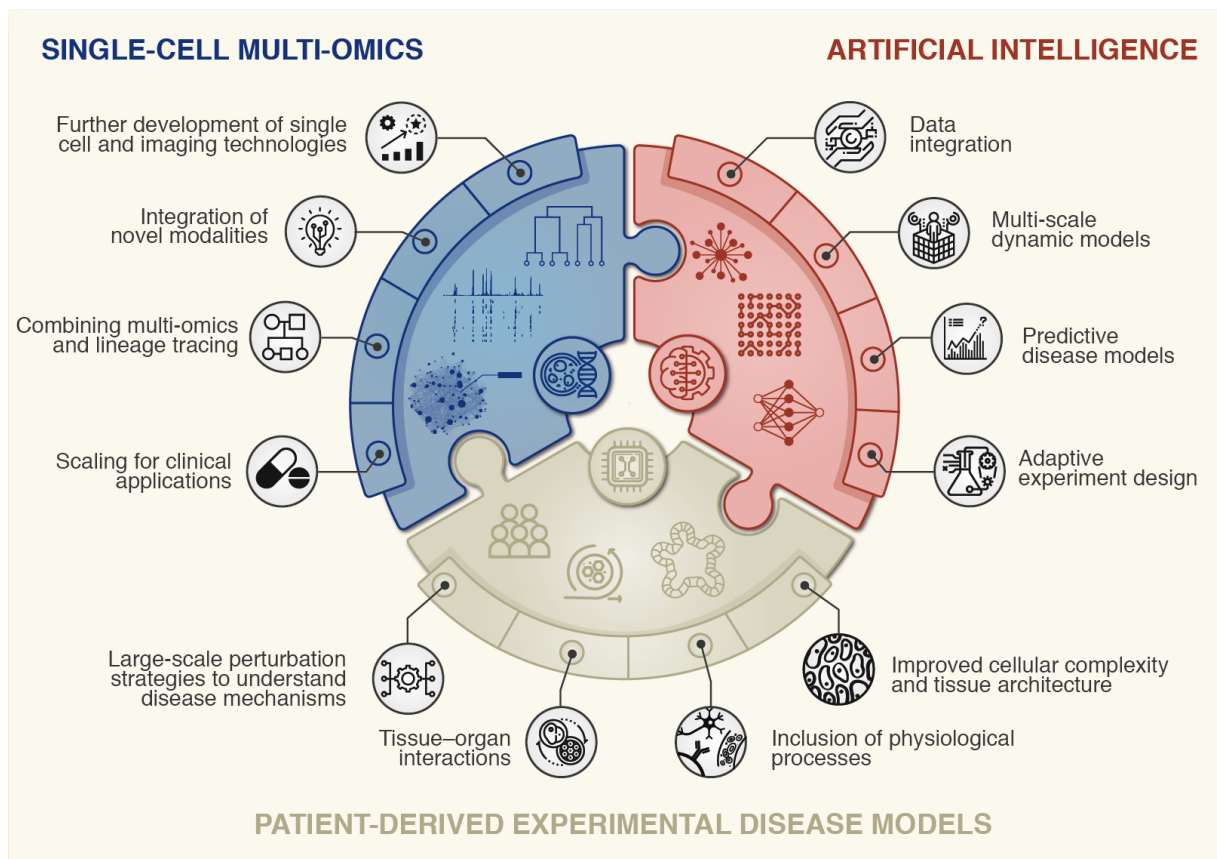
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Figure 1. Early disease detection and interception by understanding and targeting cellular trajectories through time.

(A) Cells are programmed to develop and differentiate along many different specific lineage trajectories (blue trajectories) to finally reach their functional state. When these normal lineage processes go awry, this can cause a cell to deviate from a healthy state and move towards a complex disease space (coloured manifolds defined by multi-dimensional molecular space – including gene expression, protein modifications, metabolism), as shown by red trajectories.

(B) Many diseases are only detected at a relatively late state with the onset of symptoms (red trajectory) and when pathophysiological changes can be at an advanced stage (red cells). At this point, cells, tissues and organs have undergone extensive and often irreversible molecular and physiological changes since the initial events that caused them to deviate from a healthy state. At this stage the choice of interventions may be limited and often require harsh or invasive procedures.

(C) Understanding the early molecular mechanisms that cause cells to deviate from a healthy to a disease trajectory will provide biomarkers for early detection of disease and new drug targets and innovative therapies to intercept diseases before onset of pathophysiology and manifestation of symptoms.



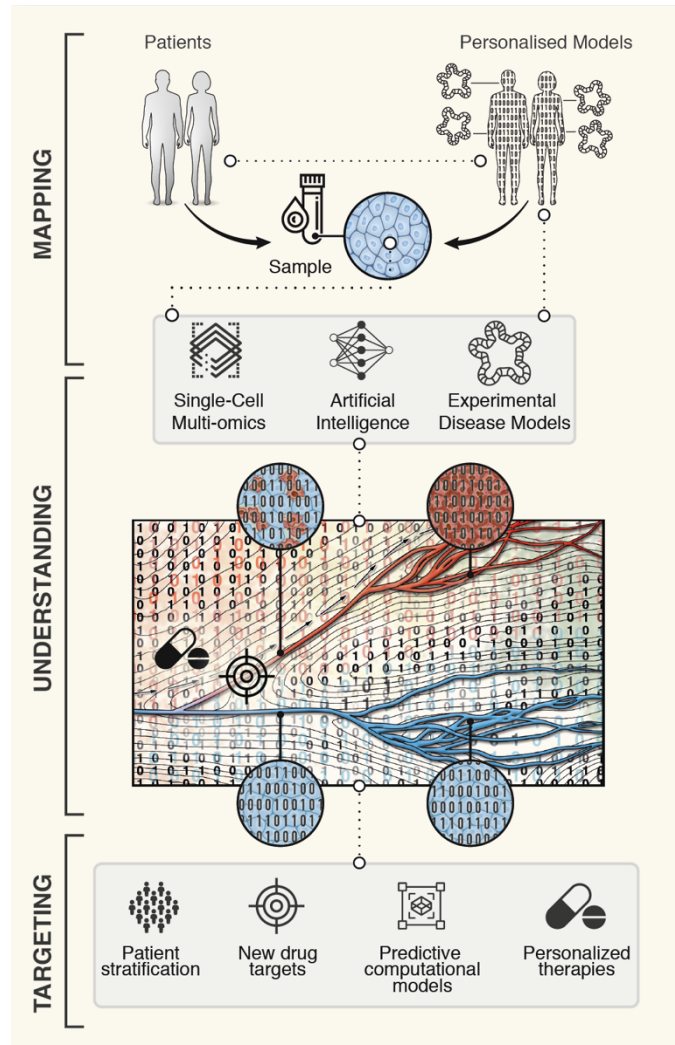
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Figure 2. Hallmarks of the LifeTime approach to disease interception and treatment.

The scheme represents the development and integration of key technologies for investigating human diseases as envisioned by the LifeTime consortium. Single-cell multi-omics and imaging technologies will be developed for high throughput applications. Different modalities are combined to provide insight into underlying mechanisms based on coordinated changes between different regulatory molecular layers. To obtain insight into cellular genealogies and cellular dynamics requires the integration of lineage tracing tools. Technologies will also need to be scaled for deployment in the clinics.

Integration and analysis of large, longitudinal multi-omics and imaging datasets will require the development of new pipelines and machine learning tools. These include development of causal inference and interpretative machine learning approaches to create molecular networks for predictive and multiscale disease models.

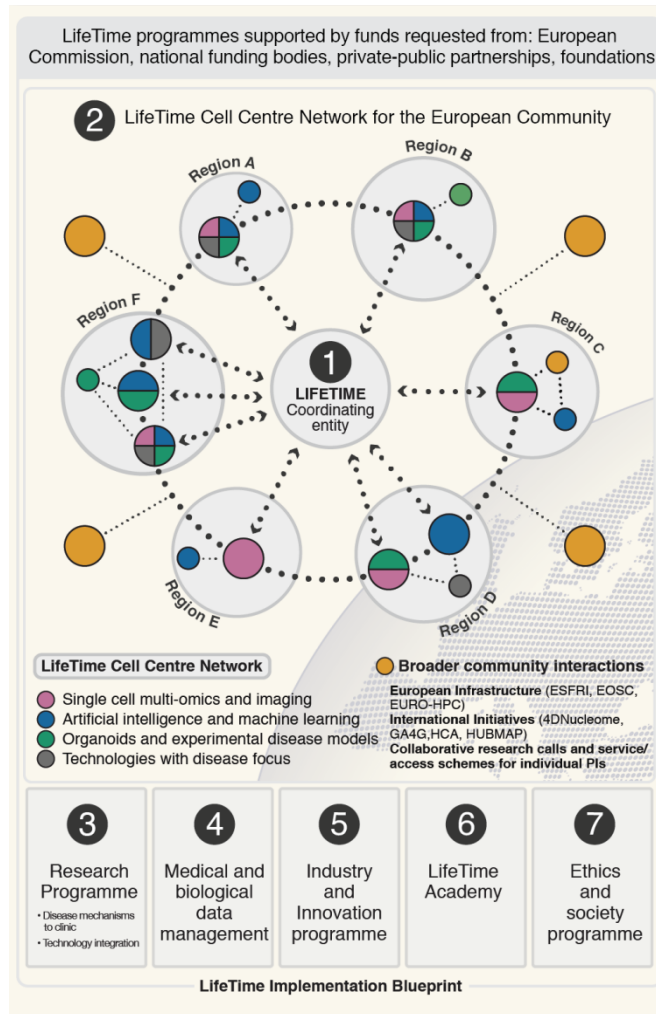
Patient-derived disease models such as organoids will be further developed to improve tissue architecture, incorporation of physiological processes, such as vasculature, nerve innervation and immune system to provide models that more faithfully recapitulate disease processes. Improved knowledge of disease mechanisms requires application of large scale perturbation tools to organoids. Tissue-tissue and organ-organ interactions will be recreated using microfluidics and organ-on-a-chip technologies to study key systemic interactions in diseases.



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Figure 3. Exploiting the LifeTime dimension to empower disease targeting.

Multi-omics analysis of patient derived samples (blood or tissue) or personalised disease models (e.g. organoids, experimental disease models) will be profiled longitudinally to cover the different disease stages. Large-scale multidimensional datasets will be analysed using AI/machine learning to arrive at predictive models for disease trajectories providing single cell resolution and molecular mechanisms of disease onset and progression. Models will be validated using large-scale perturbation analysis and targeted functional studies in disease models, which will be used in an iterative process to improve both computational and disease models.



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Figure 4. Blueprint of the LifeTime Initiative.

LifeTime proposes a large-scale research initiative to coordinate national efforts, as well as foster collaboration and knowledge exchange between the public and private sector. LifeTime recommends the implementation of several programs. (1) Community Coordination structure to avoid duplication of efforts and increase effectiveness requires funding instruments for a central coordination body (2) Network of Cell Centres to support European Community. A network of interdisciplinary centres would complement each other’s strengths and expertise in the three LifeTime technology areas and operate in tight association with hospitals, and integrate technology development with clinical practice. The connected but geographically distributed nodes would serve both as innovation hubs with strong links to industry as well as open education and training centres. (3) LifeTime Research and technology integration program. (4) Medical and biological data management platform. (5) Programmes fostering industry and Innovation. (6) LifeTime Academy. (7) Societal engagement.