2.2.9 Enabling technologies & infrastructure

This roadmap introduces (i) the Dutch Biobanking Hub (DBH), (ii) the Dutch Techcentre for Life Sciences (DTL), and (iii) a framework of advanced facilities. Together, these roadmap components offer expertise and infrastructures in life sciences technologies and biobanks, readily accessible for industry and academia. The expertise and infrastructures in enabling technologies and biobanking have a scope beyond LS&H by providing necessary technological infrastructure to other Topsectors, including Agrofood, Horticulture, Chemistry, HTSM, and Biobased Economy. In this LS&H roadmap for Enabling Technologies and Infrastructures (ET&I) we focus on the contribution to Topsector LS&H.

1. GOALS

Life science strategies have proven very effective in tackling contemporary health issues. Their translational approaches provide deep understanding at the molecular level of the causes of disease and effects of therapies. LS&H research contributes to a more efficient, cost-effective and patient-centered healthcare system based on disease prevention, more accurate diagnostics, more focused treatments, and improved efficacy and safety of drug treatment in line with the 3R (Replace, Refine and Reduce) principles.

In this research-intensive sector, technological advances in combination with a strong infrastructure are essential in accelerating innovations in each link of the LS&H chain: prevention, diagnosis, cure and care. To reduce costs and at the same time enable personalized treatment, progress depends on having access to well integrated life sciences technologies.

This roadmap aims to deliver top-level expertise and infrastructure in molecular technologies and biobanking. The cross-sector approach will enhance knowledge transfer between Topsectors and will facilitate prioritization of investments in biobanking and technology research infrastructures on a national scale.

2. ACTIVITIES

A. ET&I components

The roadmap builds on three components: the Dutch Biobanking Hub (DBH), the Dutch Techcentre for Life Sciences (DTL), and a distributed facilities framework (DFF), responding to the requirements of the LS&H roadmap as well as those of other Topsectors with a bioscience component (Fig.1).

Dutch Biobanking Hub (DBH)
Three complementary large biobanking infrastructures (1, 2), *i.e.* (i) Biobanking and Biomolecular Research Infrastructure NL (BBMRI-NL), (ii) the String of Pearls Initiative (PSI) and (iii) LifeLines, will be integrated into one Dutch Biobanking Hub with high-quality clinical and molecular data, phenotypic information, and optimized accessibility. Combining PSI, LifeLines and BBMRI-NL integrates the Netherlands biobanking activities and greatly enhances the power for developing and validating clinical findings and translating these into programs for disease prevention and targeted drug discovery

research in collaborations with industry and academia. This will further strengthen the frontline position of the Netherlands in biobanking and translational R&D in an international setting.

BBMRI-NL currently includes approximately 150 Dutch biobanks that together contain different types of biological samples from over 500,000 individuals, including over 400,000 DNA samples.

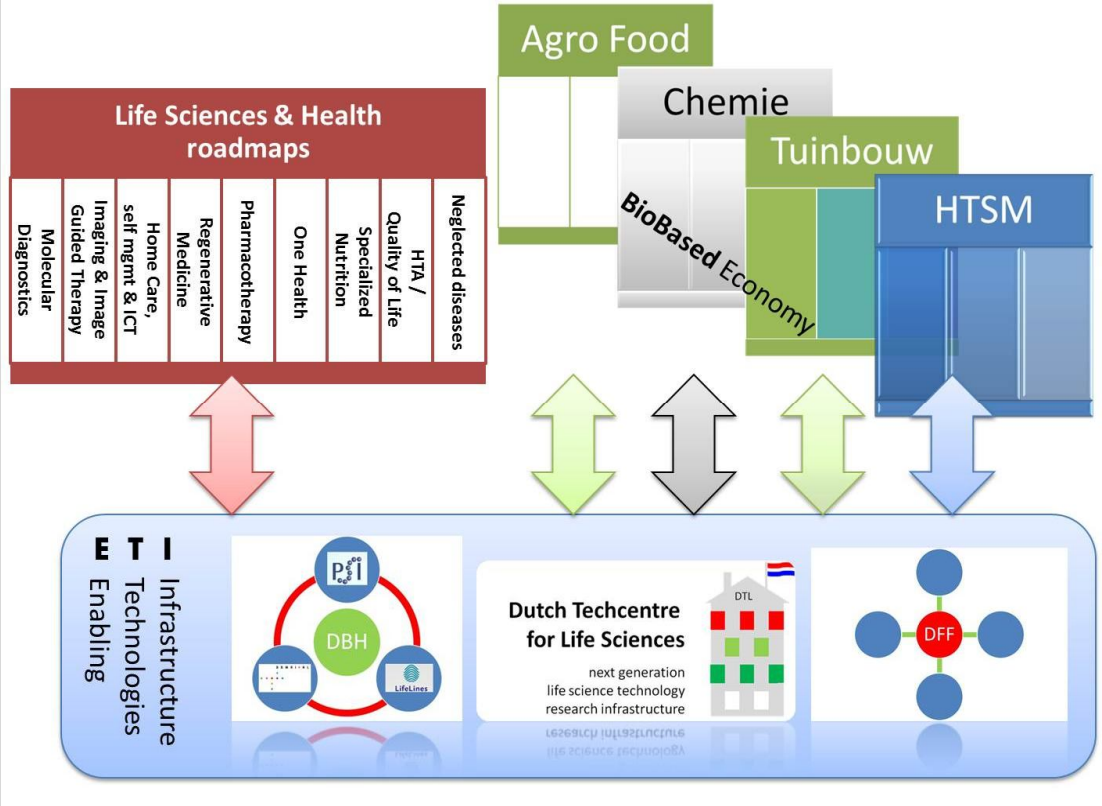

Fig. 1 Enabling Technology & Infrastructure components in the Topsectors.

Dutch Techcentre for Life Sciences (DTL)
The Dutch Techcentre for Life sciences (DTL) is founded by - and builds on - six national scientific centers with a strong technological basis: (i) next generation sequencing (CGD), (ii) proteomics (NPC), (iii) metabolomics (NMC), (iv) advanced microscopy (NL-BioImaging AM), (v) bioinformatics (NBIC), and (vi) systems biology (NCSB). DTL builds on best practices and expertise developed in these centers of expertise. DTL offers high-end enabling technologies (expertise, services, equipment and training) in the life sciences in general and in the field of health-related R&D in particular. DTL expertise and infrastructure is accessible for research institutes, hospitals and industry, with a specific proposition towards SMEs. DTL encompasses a broad network of expertise and facilities that is already involved in major public-private life science programs, and therein well-connected with over 70 SMEs and large companies.

DTL combines its technology portfolio around the functional and structural molecular organization of living systems. It has the capacity to integrate the analysis at the DNA/RNA level with subsequent levels of molecular organization and regulation (proteins, metabolites, supra-molecular (and cellular) structures). DTL thus offers integrated technological approaches in next-generation sequencing (NGS), proteomics, metabolomics and advanced microscopy, and includes bioinformatics and systems

biology to streamline the analysis, integration and stewardship of life science data. DTL develops dedicated technology applications for industry and academia, responding to the needs of the health care system as detailed in the LS&H Topsector roadmaps.

Of course, novel technologies will emerge in the international fields to complement (or replace) the high-end technologies of today. DTL includes an active policy to continuously scout and select emerging technologies that fit in the DTL portfolio. With a primary selection of the international (scientific) quality of the associated community, selected new technologies must have a strong potential within the LS&H and other Topsectors, and be able to adopt the DTL strategy to set up enabling technology facilities.

Distributed Facilities Framework (DFF)
The Netherlands has a number of ultramodern research facilities that are accessible to third parties. Examples are the high-throughput screenings facility and compound data library in Oss. Combining these with libraries of TI Pharma, the Netherlands Toxicogenomics Centre (NTC) and the national infrastructure 'NL-OPENSCREEN' of small molecule libraries, will be important to find leads for the targeted disease areas. BioConnection, offers young and innovative biopharmaceutical companies access to state-of-the-art GMP facilities and a broad range of support services, and acts as an interface for expertise that is needed to successfully complete clinical trials and production to GMP standards. EATRIS-NL will provide access to distributed infrastructure for translational research in the area of (molecular) imaging, vaccine development, advanced medicinal therapeutic products (stem cells, tissue engineering) and biologics. The Central Veterinary Institute in Lelystad includes unique hBSL3 and aBSL4 facilities that will be part of the Emerging Disease Campus. (Transgenic) animal facilities, such as the new Center for Advanced Bioresources Services in Schaijk, might also be considered as part of the distributed facilities framework to bridge the gap between *in vitro* and human studies. Furthermore, close collaborations with the Advanced Medical Imaging infrastructure collectively represented by four IMDI core facilities will be initiated.

B. ET&I Agenda

Transition from the present fragmented situation to consolidated accessible expertise and infrastructures in high-end enabling technologies and biobanks, creates exciting opportunities in health care as it helps to deepen our understanding of health and disease-related processes. Tangible deliverables for the next two years include the sustainability of the major ET&I roadmap components in an international (European) context.

DBH
- Integration of BBMRI-NL, PSI, and LifeLines into one Dutch Biobanking Hub (DBH; Fig. 2) with high-quality clinical and molecular data, phenotypic information, optimally accessible through a centralized, privacy-protected multilevel catalogue;
- Linking biobanks to medical and socio-economic registries.

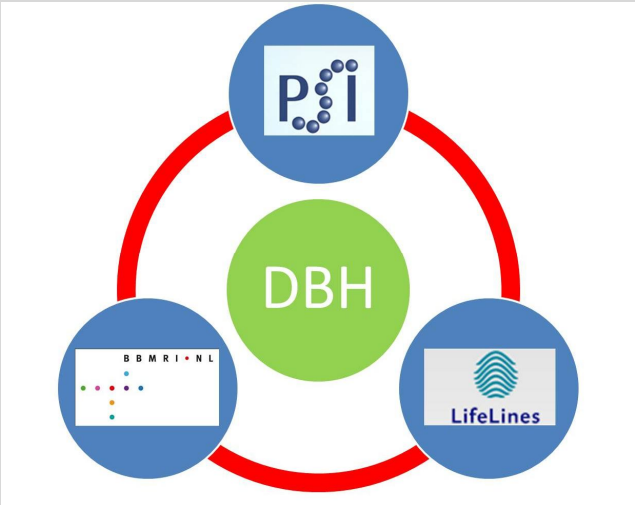

Fig. 2 Integration of biobanks in the Dutch Biobanking Hub (DBH).

DTL

Development of DTL to an international expertise and enabling technology hub completes a process started in 2008 (Fig. 3).

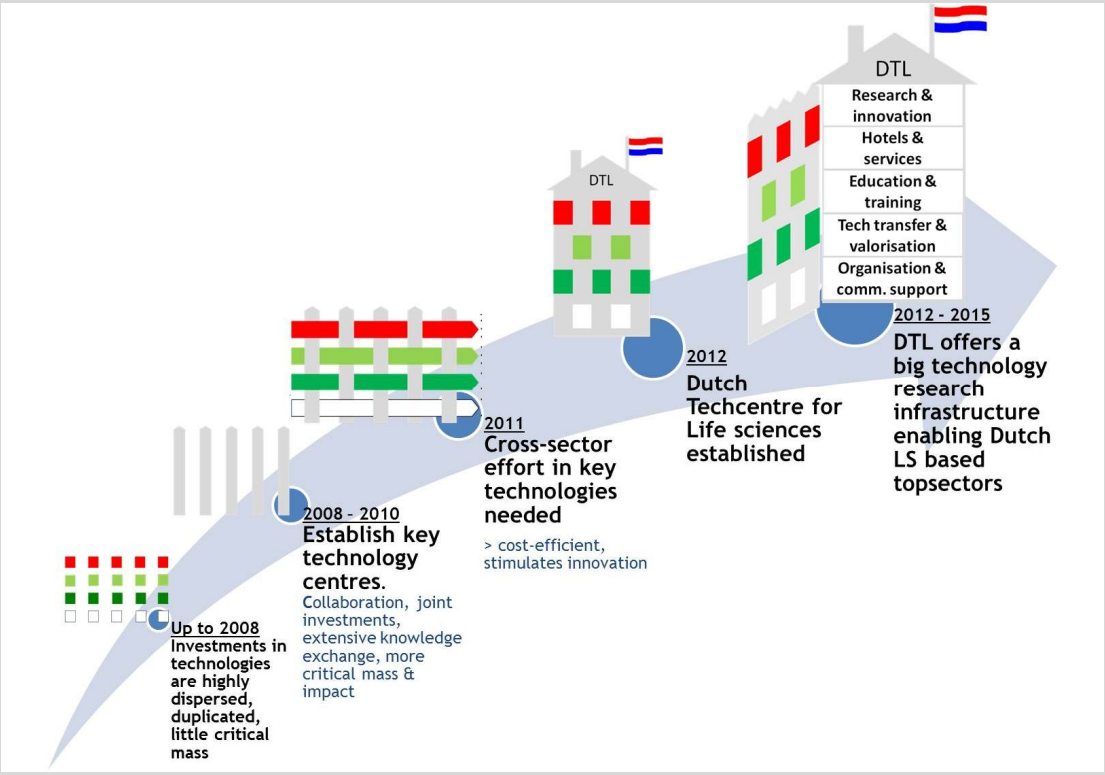

Fig. 3 Development of DTL from fragmented technology activities to a big technology research infrastructure.

Key to the development of DTL are the establishment of nation-wide enabling technology centers, collated in DTL and strongly embedded into European initiatives.

- Advanced microscopy infrastructure (NL-BioImaging AM);
- Proteomics research facility (Proteomics@work);
- Data Integration and Stewardship Centre (DISC ELIXIR) including the Translational Research IT infrastructure (TRaIT);

- Next-generation sequencing expertise network for genomics and epigenomics research;
- Metabolomics analysis network.

An integrated ET&I approach
- Cross technology research;
- Linking of the biobanking infrastructure with the enabling technologies;
- Application of enabling technologies and infrastructures in the LS&H Topsector and diverse healthcare-adjacent areas such as toxicology/safety, nutrition, epidemiology, alternatives for animal testing;
- Application of enabling technologies and infrastructures cross Topsectors;
- A human capital agenda aiming at education and training.

C. ET&I Activities: Type of R&D

The ET&I roadmap will provide enabling technologies and infrastructures for the other LS&H roadmaps and other Topsectors (as depicted in Fig. 1). ET&I activities will range from fundamental research to concrete applications in health care. Patient and biobank-based studies and enabling technology-driven research will result in diagnostic and clinical applications. To this end, public-private partnerships between individual biobanks, enabling technology centers and industry already exist and will be extended. In addition, expert centers are being developed, establishing public-private partnerships in the pre-competitive, not-for-profit field.

There are strong links with activities of other LS&H roadmaps, including:
- **Molecular diagnostics.** Integration of molecular diagnostic technologies and tools to provide straightforward diagnoses in a complex biological context facilitates the development of candidate biomarkers into validated molecular diagnostics in clinical use.
- **Imaging and image-guided therapy.** Advanced Microscopy provides the resolution to reveal the molecular and cellular details necessary for understanding the biological mechanisms of human diseases, pre-clinical drug screening and optimization of treatment approaches.
- **Homecare & self-management.** The development, evaluation and implementation of technological solutions that will contribute to a sustainable healthcare system for people with chronic diseases or disabilities, is central to this roadmap.
- **Regenerative medicine.** Approaches presently under investigation employ the complete multidisciplinary toolbox of contemporary cell and molecular biology, materials science and bioengineering.
- **Pharmacotherapy.** This roadmap, comprising therapy development for rare diseases, chronic and complex diseases, and infectious diseases, is the home base of the translation of life science discovery into future heath care. It is critically dependent on the technological and human resources and expertise available in the Enabling Technology Infrastructures.
- **One Health.** Developments in vaccines, diagnostics and other interventions depend on a number of enabling technology platforms. Examples are -omics, molecular diagnostics and imaging.

- **Specialized nutrition, health and disease.** The management of these multi-factorial diseases needs a new and integrated therapeutic approach based on appropriate phenotyping and by combining early diagnostics *etc.*

The integrated ET&I research approach provides novel solutions in the 'prevention-diagnosis-cure-care' chain. Integrated data sets from key enabling technologies are essential to identify and measure personalized parameters that mark predisposition and onset of disease (*prevention*). Identifying and measuring critical disease-related parameters, using a broad range of technologies, allows personalized diagnostics, monitoring, and prognosis (*diagnosis*). Highly advanced technologies may be integrated in the care system improving the cost/benefit ratio (*care*). A convergent healthcare infrastructure, integrating biobanking with prospective treatment monitoring, allows optimizing therapeutic efficacy and reduces costs of ineffective treatment (*cure*).

Current predictive models for human drug safety and efficacy are not sufficiently reliable. To narrow the translation gap, development and implementation of innovative technologies that better (i) predict the health developments, (ii) prevent adverse health effects, (iii) shorten the time to "first-into-human" phase, and (iv) are preferably non-animal-based, are urgently needed. Such models would require data from innovative genomics technologies, life cell imaging and data analysis and integration to improve, in collaboration with the Biobanking research infrastructure, translation to human diseases, therapeutic interventions and human drug-induced toxicities.

Not only cryo-preserved human tissues, but preferably fresh human tissue and primary cells cultures should become available to the life sciences sector, preferably through dedicated, high quality bio-banking. These materials are needed to improve the predictability in the different phases of development; for screening of efficacy and for safety testing.

3. CASE

A. Priorities

The Netherlands has an acknowledged leading international position in life sciences-related R&D. The high quality ET&I technologies and infrastructures are essential to sustain and expand that position.

- ET&I *accelerates innovation* in the life sciences.
  - It gives academia and industry easy access to high-end technologies, biobanks, expertise, materials and a distributed framework of facilities.
  - The cross-Topsector focus of ET&I drives innovation by bridging fields.
- ET&I *accelerates development* of key technologies and expertise.
  - Dedicated technology research and development accelerates talent development, boosts international lead position and attracts industrial involvement.
- ET&I *boosts commercialization* of key technologies and expertise.
  - Supported by a dedicated Open Innovation structure, attracting top scientists and top commercial activities due to its excellence and international stature.
  - ET&I centers provide test/demo sites for novel equipment and technologies by creating a market place for vendors and applications.

The combination of readily accessible key technologies, biobanks, expertise and materials will substantially contribute to more cost-efficient health care in the Netherlands. Below a few examples.

- ET&I will enhance the rate of drug development, including regulatory acceptance, by giving Dutch academia and industry access to a high-end technology and expertise platform that is able to analyze and integrate multiple diverse data sets (genomics, proteomics, metabolomics, microscopy), giving detailed and patient-specific insight into the (mal)functioning of cells, tissues and complete human beings.
- The integrated approach is strongly enhanced by combining ET&I technologies with ET&I biobanks and DFF facilities. Together, ET&I creates an accelerated translational road towards evidence-based and personalized health resulting in cost reduction by reducing trial & error in curative interventions, thereby decreasing the burden for patients.
- Concentration of investments in high-end technologies, biobanks and expertise in a limited number of (distributed) national centers will result in cost reduction and enhanced accessibility of infrastructures and expertise.
- Besides direct economic benefits, there are also a major societal benefits due to the improvement of the quality of life by improved efficacy and safety predictions, diagnosis and treatment, and proper counseling. Although harder to quantify, improved diagnostics (often leading to the relief of concerns), proper counseling and well-targeted therapy all greatly improve the quality of life of patients, people at risk, their families and caretakers.

B. Strengths

Creating focus, critical mass, synergy and excellence in enabling technologies and biobanks in the Netherlands responds to the international trend of concentration of high-end expertise and infrastructure in the life sciences in a network of a limited number of national institutions. The ESFRI program is an exponent of this trend. The Netherlands has the opportunity – based on an excellent starting position – to harbor several of such hot-spots dedicated to the LS&H arena. This development strongly

contributes to a Dutch open innovation environment with an ambition to compete with e.g. the Boston area. In the context of the ET&I roadmap this is underscored by the fact that BBMRI and DTL are deeply involved in European initiatives: ELIXIR, Euro-BioImaging, BBMRI, EATRIS, ISBE, INSTRUCT and Prime-XS. This development is a pay-off of sizeable investments of the Dutch government in life science research, biobanks and enabling technologies over the recent years (4).

The Netherlands has a strong tradition of collecting clinical and population samples into biobanks and making them available to the LS&H communities. The high quality, diversity, quantity and accessibility of data and samples, combined with their level of organization and willingness to cooperate, the Dutch biobanking community has given the Netherlands a key position to create momentum in this field at the international level.

Molecular diagnostics is one of the fastest growing segments in the healthcare industry. The value of ET&I expertise and infrastructures in technology and biobanks is increasingly acknowledged by industry. Given the steeply rising cost per successfully developed drug, the availability of an integrated resource in the Netherlands is essential. In this context ET&I facilitates research by making available a wealth of bio-samples and related clinical and molecular data for translational medical research. Technologies and expertise to analyze and integrate large and complex data sets, proper access to protocols and the development of computational models for predicting drug efficacy and safety, should attract large international funding to the Netherlands. These ET&I efforts will breed new synergies between the industry and academia, thus providing ample opportunity for IP development.

In the above context, cooperation with industry, including large pharma, has already been initiated. Apart from investments from health-oriented industries and public-private consortia, ET&I particularly strengthens the Dutch biotech SMEs, not only in the field of diagnostics and drug development, but also in software, and data stewardship, analysis, sharing, and integration.

4. CONNECTIONS

ET&I partners are already firmly embedded in several public private partnerships or other types of collaborations (Fig. 1 and Fig. 4).

A. Connections to other roadmaps within Life Sciences & Health

ET&I provides expertise and infrastructures in enabling technologies and biobanks for all other roadmaps within LS&H (Fig. 1.).

B. Connections to other Topsectors

ET&I offers technologies, infrastructure and expertise to understand life at the molecular level, regardless whether this is human, plant or microorganism. Thus, ET&I has natural links to several other Topsectors and their research and innovation agendas (Fig. 1), including Chemistry, Horticulture, Agrofood and High Tech.

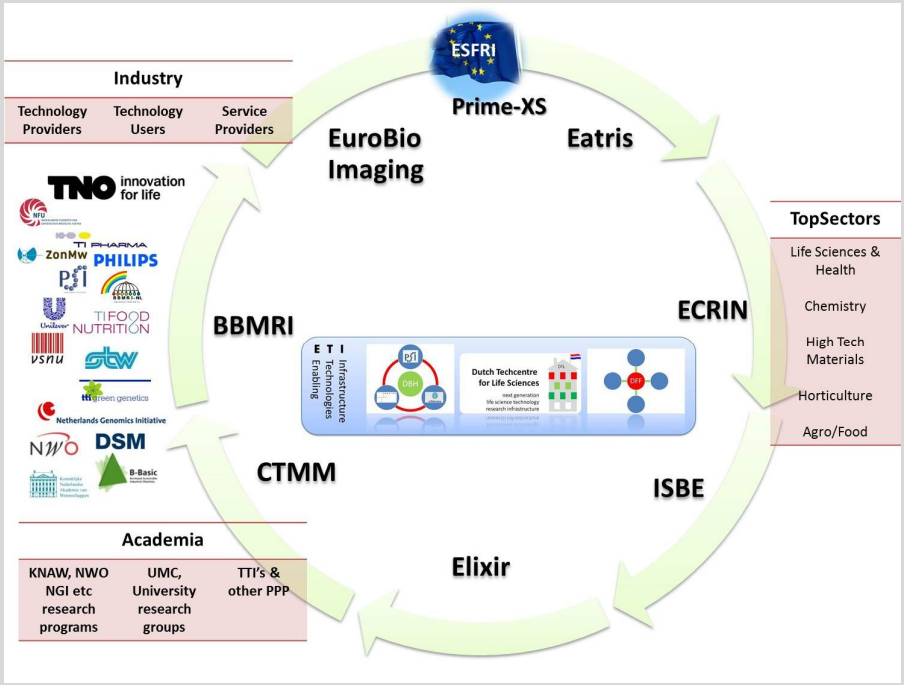

Fig. 4 ET&I components in their national and international setting

C. Connections to existing programs & initiatives

DBH

- BBMRI-NL received initial funding from the NWO National Roadmap program in 2008. There is insufficient funding to achieve all goals, as initial start-up funding was granted for only 3 years, although with the intention of a follow-up.
- PSI has been funded by a five-year FES grant of the Dutch government, which expires at the end of 2011. The NFU has decided to continue the support, but at a lower level which requires transition from the project phase to a more regular organization embedded in the UMCs. The sequel focuses on maintaining and consolidating the infrastructure and to embed the practices in all UMCs, with operation costs guaranteed by the UMCs. Additional funds are needed in the coming years to expand the scope with new disease pearls.
- LifeLines is funded partly by FES, partly by other sources and has funding until 2015. Given the scale of the project and its duration of a few decades in forthcoming infrastructure calls, additional funding is required.

DTL

- DTL techcentres are consortia in the NGI program (funding until 2013): Netherlands Proteomics Centre (NPC), Netherlands Metabolomics Centre (NMC), Centre for Genome Diagnostics (CGD), Netherlands Bioinformatics Centre (NBIC) and Netherlands Consortium for Systems Biology (NCSB). DTL is completed with the expertise and technology of NL BioImaging AM.
- The Netherlands Proteomics Centre (NPC) is coordinator of a FP7 funded European Large Scale facility for proteomics: PRIME-XS.
- ET&I partners are well-embedded at the European level, playing a leading role in multiple European initiatives such as: ELIXIR (bioinformatics), BBMRI-NL (biobanks), EATRIS (translational research), EuroBioImaging (imaging), INSTRUCT (structural biology), and ISBE (systems biology) (3).

Other programs relevant for ET&I roadmap

- Other relevant programs include the NGI LS@Work program for starters in the life sciences, the ZonMw program Translational Research, in which first in-human studies are funded, and the NWO Centres for Systems Biology Research.
- Investment subsidies NWO-Groot and NWO-Middelgroot will often be relevant cross Topsectors.
- Many of the roadmaps focus on translational and applied research. Fundamental research drives new ideas and innovation. Relevant programs in this respect are the NWO and ZonMw Open Programs and the NGI Horizon program.

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