Synopsis of the HCEMM project

Executive Summary

Despite increasingly available funds and presence of talented young and senior scientists, biomedical research in Hungary lags behind Europe both in terms of competitiveness and its ability to quickly adapt to the rapidly changing technologies and to the cooperation-driven post-genomic era.

The main goal of creating the Hungarian Center of Excellence for Molecular Medicine (HCEMM) is to develop an autonomous, game changer organization, which can influence the research environment in a large segment of the Hungarian institutional and university environment with a long term reforming effect. Having identified the barriers and disparities hindering European level competitiveness and the challenges of the post-genomic area, **the institutions forming HCEMM have formulated the strategy for a joint research and translational program**, which is based on the available basic research potential and clinical portfolio, and eventually can deliver high impact results in the field of translational medicine.

- ✓ The local research potential and critical mass in the fields of aging related non-communicable diseases gave rise to three thematic pillars (Immuno-inflammatory diseases; Metabolic and cardiovascular diseases; Genomic instability and cancer) and three cross-cutting themes (Disease in a dish systems; Precision medicine and prevention; Units of translational research);
- ✓ Technology infrastructure and advanced core facilities will be jointly organized and managed with the primary aim to support HCEMM's research; thus Single-cell omics; Functional cell biology and immunology; and *In vivo* imaging advanced core facilities (ACF) will be developed;
- ✓ Selection and evaluation of research groups will be based on international standards using panels with outstanding field-leader researchers exclusively from international institutions;
- ✓ Research groups will have predictable funding schemes providing long term stability and attractiveness;
- ✓ Excellence will be awarded with competitive salaries and benefits.

An efficient technology transfer system will be built to facilitate utilization of intellectual property, formation of spin-off companies and cooperation with industry.

The **partnership with the European Molecular Biology Laboratory (EMBL)** and its long term experience fostering cooperation and excellence in molecular life sciences and molecular medicine will provide guidance and expertise to achieve the above goals, particularly bringing in a new research culture and management approaches including selection, regular evaluation and internationalization of productive research groups. Legally EMBL and HCEMM will be connected via a partnership agreement, an EMBL instrument already well established in Europe, which has created a network of institutes of excellence in the life sciences, including molecular medicine. A further goal of the EMBL Partnership will be the establishment of day to day collaboration between HCEMM and EMBL research groups that would allow HCEMM to become part of the EMBL partnership network. A **Scientific Advisory Panel** has been set up with already committed members from leading European institutions of molecular life sciences such as VIB Ghent, CRG Barcelona, FIMM Helsinki and Oxford University, in addition to EMBL.

Leadership of HCEMM will have autonomous decision making power in selecting and funding of excellent research groups and technology developments. This will be achieved by establishing HCEMM as a non-profit, public benefit company, which will have bilateral contractual agreement with the institutions hosting the research groups and core facilities. The Center will have a distributed organizational structure having its headquarters in Szeged and two complementary nodes located in Szeged and Budapest. This distributed structure is a great advantage for translational research as it offers access to the patient population served by the largest clinical hospitals of the country (which are also university teaching hospitals for the medical faculties).

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The organizational and management model of HCEMM favors the flourishing of research groups operating in a flat structure and integrated around the three pillars of the research focus. The management and administration, together with HCEMM research groups, will be hosted in Szeged in a new research building next to the recently built laser center Extreme Light Infrastructure Attosecond Light Pulse Source (ELI ALPS) of the EU providing unique opportunities for collaborations and vibrant international scientific environment.

Financial stability of HCEMM will be based on three major components during the first 7 year period, amounting together to ~52 million euros. This is made up of the H2020 Teaming support for catalyzing the transformative changes (29%), Hungarian structural/government funds (43%) and earmarked financial contributions from the founding organizations of HCEMM (28%) given from their own non-governmental income. For long-term sustainability, continuation of funding will be requested based on meta-evaluation of the achievements of HCEMM by international expert panels. Outcome of this evaluation will be the basis of the ongoing financial support of the government and the founding institutions. (This will be carried out for a first time at five years after HCEMM starts to operate.). In addition, gradually increasing income is predicted from diverse grant schemes available in Hungary and Europe, from technology transfer, and from industrial collaborations and services.

It is expected that HCEMM will be a strong catalyst of reformative changes in biomedical science and in institutional research management, and will serve as a model in the country and possibly in the Central-Eastern European region for organizing research in other science areas. Furthermore, it will take part in the wide-ranging social debate on the scientific and technological aspects of fast advancing molecular medicine. It will also act as a catalyst to kick-start the dialogue between researchers and will encourage cross-fertilization of their ideas in order to contribute to the scientific knowledge generation and transfer of knowledge to the private sector.
The concept of setting up HCEMM is fully aligned with the vision, national and horizontal priorities and county specifications highlighted in the Smart Specialization Strategy of Hungary and provides a response well fitted to the challenges and needs identified therein.

Mission, Goals and Values of HCEMM

Mission

HCEMM has the mission to become an internationally recognized institute of excellence promoting molecular medicine, providing autonomy, transparent policies, financial stability and modern infrastructure for excellent scientists.

Goals

1. to develop an autonomous research institute that has the ability to contribute to the renewing the Hungarian research and innovation system: establishment of the Hungarian Center of Excellence for Molecular Medicine
2. to improve the international standing of Hungary in the field of molecular medicine in a strong partnership with the European Molecular Biology Laboratory
3. to provide scientists with cutting edge technologies, opportunities for cross-fertilization and autonomy as well as freedom to conduct innovative research
4. to actively contribute to the education and training of researchers in the area of molecular medicine by providing multi- and inter-disciplinary training for the next generation of scientists
5. to promote cooperation with industry by ensuring the transfer of technology and knowledge to industry based in Hungary and Europe, by promoting research groups to form spin-off companies, by attracting and carrying out industrial research projects, by generating and providing funding opportunities in related translational projects with associations or companies to make contribution to sustainable development and value for society
6. to take part in the wide-ranging social debate on the scientific and technological aspects of molecular medicine, by actively engaging in objective communication on science, with a focus on educating the public and being receptive to their needs

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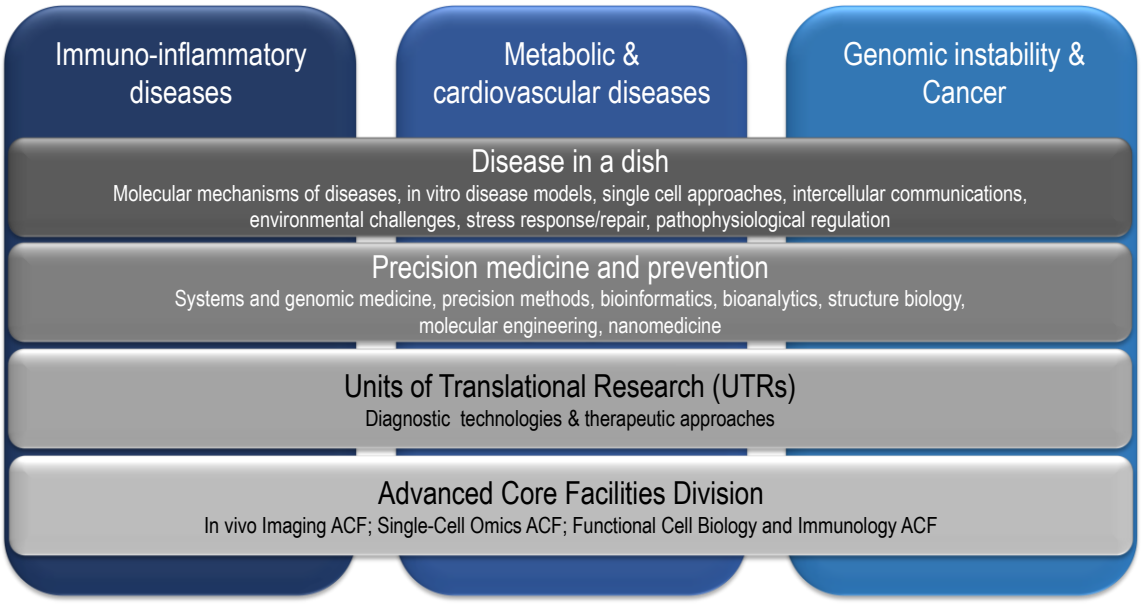
Values

- ✓ Excellence
- ✓ Scientific autonomy
- ✓ Cross-fertilization
- ✓ Equal opportunities
- ✓ Sustainability and transparency
- ✓ Enabling innovation
- ✓ Internationalization

Scientific and Innovation Strategy of HCEMM

In order to enable the sound execution of our mission, a **Scientific and Innovation Strategy** which responsive of our goals and reflective of our values, was formulated. To account for feasibility, the existing scientific research base relevant to internationally competitive research in the field of molecular medicine was evaluated at research institutions, which establish the HCEMM. Furthermore, the process included consultation with scientific experts of EMBL to create a strategy that is readily embedded in current trends in molecular life sciences in Europe. To facilitate long term sustainability, alignment of the proposed strategy was assessed with relevant programs at the national and EU levels. It has been concluded that HCEMM should focus on and support molecular medicine-oriented research activities targeting key, highly prevalent ageing-related non-communicable diseases.



The strategy (see Figure above) is based on three thematic pillars (these thematic pillars are organized into divisions) and three cross-cutting horizontal themes. Of further importance, high quality excellent research would be most efficiently (but not exclusively) supported by establishing a matrix of advanced core facilities (ACF) in the HCEMM.

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Thematic pillars

The thematic pillars are highly complementary and synergistic in terms of the underlying concepts and research approaches. Moreover, all imply similar needs for high-end technologies and core facilities. Finally, they represent strong research areas in Hungary and a number of already existing excellent Hungarian groups will create a 'seed incubator environment' of scientific excellence (research, infrastructure, education) that is essential for HCEMM's development (see Figure above and also the below sections).

☑ Immuno-inflammatory diseases

During the past decade, novel revolutionary frontiers have been opened at the immuno-inflammatory research fields. Indeed, with the help of modern, state-of-the-art technologies (immunomics and other omics, systems biology) it was identified that the immune system is much more complex than previously thought and that its proper functions are defined by multi-directional intercellular communications between cellular (and humoral) components of innate and adaptive immunity. Furthermore, it was also unambiguously shown that the homeostatic regulation of the immune-inflammatory responses is fundamentally dependent on constant communication with the highly versatile (and also very complex) microbiota inhabiting the barrier surfaces of the human body. Of further importance, extensive research efforts of the past decade have also revealed that altered immunological and (chronic) inflammation-related regulations play key roles in the pathogenesis of multiple cardiovascular (e.g. atherosclerosis) and metabolic (e.g. obesity) diseases, as well as, in cancer initiation, development, and progression. No wonder, therefore that immuno-inflammatory (either 'classical' or related) diseases are now considered as the most prevalent human pathologies. The complexity of the immune system requires novel therapeutic strategies to manage the immuno-inflammatory conditions. Most importantly, novel, combined and personalized pharmacological, biological, and (possibly) gene therapeutic efforts are suggested. However, we are convinced that these combined therapeutic protocols could only be successful if future research activities systematically and mechanistically uncover the (often redundant) genetic, transcriptomic, molecular, cellular and intercellular immune signaling pathways. Moreover, define those functional patterns whose genetic or acquired alterations could lead to the manifestation of the given pathological condition.

☑ Metabolic and cardiovascular diseases

Metabolic and cardiovascular (CV) diseases are among the major cause of death in Hungary and worldwide, thus impose an enormous social and economic burden. In the clinical practice there is a great need for i) the elucidation of the molecular pathomechanism of such high-burden diseases (including obesity, diabetes, heart failure), as well as for ii) the development of novel therapies, cost-effective treatments and iii) more personalized or at least targeted therapeutic approaches. This is especially true for the chronic, most often ageing related cardiovascular and metabolic diseases. As an example, due to landmark development of invasive technologies of the past century, the efficacy of successful clinical management of acute cardiovascular conditions (e.g. heart attack) has significantly improved. However, in parallel with an increase in life expectancy (largely due to the improved therapy of acute heart conditions mentioned above), the field now faces a serious problem of chronic cardiovascular diseases (such as e.g. chronic heart failure). As these ageing related conditions are characterized by very complex pathomechanisms involving metabolic and immunological alterations, as well as subcellular, cellular and tissue remodeling, it is very important for research-oriented, industrial and governing bodies to realize that the mechanistic and/or molecular understanding of such high-burden diseases is at least as important for next generation medicine as are the direct conventional clinical treatment efforts. We are concerned that a better genetic, transcriptomic and molecular characterization of CV diseases is a key element of this process.

☑ Genomic instability and cancer

In the EU-28, cancer accounts for 25.8% of the total number of deaths, acquiring the second position behind cardiovascular diseases. In 2012, among the EU member states, the highest standardized death rates for cancer were recorded in Hungary and Croatia, both with rates over 330 per 100 000 inhabitants (EuroStat data). During the past decade(s), significant developments have been made to lower the burdens related to cancer and its

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complications. Indeed, since 2005, more than 60 anticancer drugs have been approved by the FDA, which include novel chemotherapeutic agents, humoral and cellular immunotherapy applications, as well as high-end targeted cancer therapy protocols (e.g. angiogenesis inhibitors, modulators of specific and multiple molecular pathways). In addition, significant progress has been achieved in cancer prevention (e.g. cervical cancer vaccine) and screening (e.g. breast and prostate cancer). Yet, despite these tremendous efforts and advances, cancer is still a rapidly growing burden (especially in the ageing societies) and remains a public health problem world-wide. Our vision is that the lack of break-thought translational developments in the field is due to the extreme heterogeneity of malignant diseases. We are convinced that this can only be combatted successfully if one employs novel, alternative and multidisciplinary approaches which include combinations of personalized, precision and systems medicine, as well as of multilevel 'omics' including genomics, epigenomics, metabolomics, single-cell analysis, lipidomics, etc.. Of further importance, since cancer is mainly a genetic disease caused by mutations in DNA leading to inherent heterogeneity at the cellular and molecular levels, intensive research efforts should be invested to assess the genetic material of the tumor cells. These studies can help in identifying such cancer-related novel, key genes or genetic variations which may function as future therapeutic targets and/or validated tools for early detection, diagnosis, and prevention.

Cross-cutting themes

The above themes will be accompanied by three novel and innovative cross-cutting themes. These themes are technology driven and are expected to serve, support and strengthen the three thematic pillars – not only technically, but also conceptually –, thereby enabling higher impact and translational activities. Similarly to the thematic pillars, focuses of the horizontal themes have been identified based on already exiting Hungarian excellence, technical and technological expertise and feasibility – realized at the levels of both the existing research groups and the participating partner institutions.

☑ Disease in a dish

Disease in a dish" is a cutting-edge strategy that allows researchers to study an individual patient's cells in a laboratory dish. Originally, this approach was introduced to employ stem cells, especially induced pluripotent stem cells (iPS), isolated from given patients and differentiated to a designed lineage to mimic the corresponding disease. This approach can bypass the significant problems and limitations of traditional approaches (the use of cell lines and/or transgenic animal models), which evidently could not cope with the complexity of molecular medicine and hence with multiple disease-inducing factors including the genetics of the patient and environmental and epigenetic factors. However, one of the key goals of the strategy is to exceed the original "Disease in a dish" concept and hence to expand its scope. Therefore, based on current research trends and the identified Hungarian expertise, the 'revisited' cross-cutting platform now aims to uncover the molecular mechanism of certain diseases by identifying, assessing and developing *in vitro* disease models, single cell approaches, intercellular communication networks, environmental factors (e.g stressors), and pathophysiological regulatory patterns and matrices. With this complex, novel technological approach it is expected that impact of research activities carried out in the frame of the three thematic pillars can be further strengthened, especially from the molecular and translational aspects, which are the prerequisites of modern molecular medicine.

☑ Precision medicine

The biological complexity of major non-communicable diseases, such as cancer, metabolic-cardiovascular and immune-inflammatory disorders requires entirely new approaches like solutions related to systems medicine. Systems medicine, an emerging approach applied to biomedical and biological scientific research, is a true interdisciplinary field of study that focuses on both horizontal and vertical interactions within biological systems. This holistic approach is extremely well suited to cover complex biological and biomedical events in health and disease. For instance, the Human Genome Project is an example of applied systems thinking in biology, which has led to new, collaborative ways of working on problems in the field of genetics. One of the outreaching aims of systems biology is to model and discover emergent properties; typically those involving metabolic- or cell signaling networks, providing direct links to pharmacological discoveries. However, the concept of state-of-the-art precision medicine goes far beyond systems biology and medicine. Indeed, modern, personalized and

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'targeted' medicine approaches require (among others) high-end bioinformatics, 'big data handling', and bioanalytics, as well as cutting-edge technologies of structure biology, molecular engineering, and nanomedicine. As these emerging fields of basic and applied science are identified as technological strengths of the participating Institutions of the HCEMM, they perfectly complement and further support the thematic research activities.

☑ **Organization of Units of Translational Research (UTRs)**

The ultimate goal of molecular medicine research is to translate the scientific findings and results to putative clinical applications – as closely to human conditions as possible. Therefore, the establishment of multiple UTRs is a core component of the HCEMM organization. Logistically, by creating UTRs, formally designated collaborative research groups will emerge which will include both participating practicing clinical scientists, and experts of the molecular medicine field. These laboratories would carry out translational projects, in which basic-applied research activities will be accompanied by significant clinical components. The infrastructural and conceptual bases of UTRs are already available at the large University Hospitals of the participating Institutions. Specifically, the following 'translational strengths' were identified: Semmelweis University for translation research of cardiovascular and metabolic diseases; University of Szeged for translational research of infectious, immunological and inflammatory diseases. With the organization of the novel HCEMM, these currently separated entities (besides their evident improvements) will be coordinated by the Headquarter; moreover, if deemed necessary throughout the continuous evaluation of the HCEMM, new UTRs with novel focuses will also be established. Hence, the joint operation and constant development of UTRs at the different nodes of HCEMM will lead to a major competitive advantage by offering immediate and non-restricted access to human data, biological samples of patients, as well as a relatively easy path to clinical trials and drug development. Collectively, this unique set-up will result in clear advantage and impact for not only basic, applied and translational scientists but also for pharma and biotech partners.

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