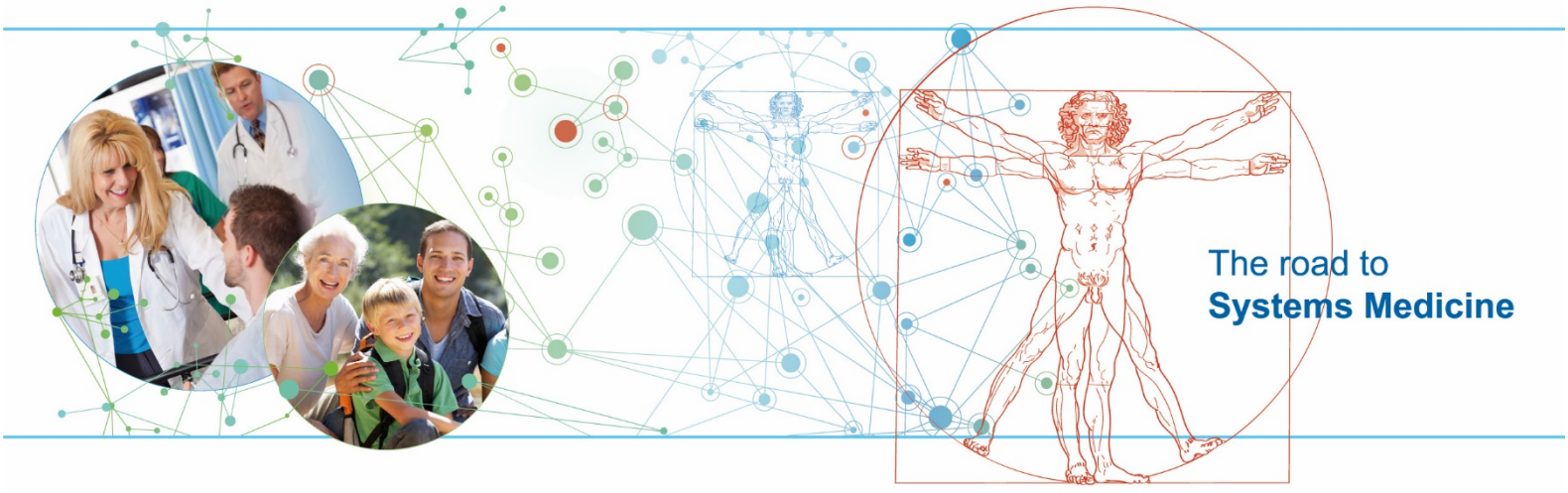
Coordinating Action Systems Medicine
Implementation of Systems Medicine across Europe



Common initiatives in Systems (Bio-)Medicine

CASyM workshop report

February 2016

IMPRINT

Authors

Regina Becker and Clemens Ostrowicz
Luxembourg Centre for Systems Biomedicine (LCSB), Luxembourg

Date

February 2016

Contact information

Regina Becker
Luxembourg Centre for Systems Biomedicine
regina.becker@uni.lu

Publisher

CASyM administrative office
Project Management Jülich, Forschungszentrum Jülich GmbH
m.kirschner@fz-juelich.de

TABLE OF CONTENT

PROOF OF CONCEPTS IN SYSTEMS MEDICINE

Success stories in Systems Medicine

Mikael Benson, The Centre for Individualized Medication, Linköping University Hospital, SE, CASyM steering committee, CASyM Deputy Speaker

Presentation abstract

Currently, early and individualised diagnostics are the core of successful applications of Systems Medicine approaches. Strong advances in this respect have for example already been made in the fields of neonatal screening, rheumatoid arthritis and asthma. However, instead of broad application of such approaches, reality is still characterised by late start of treatment and lack of efficient diagnostics to stratify patients resulting in inefficient therapies and drugs, which drive costs in health care and drug development. Given the long development of several especially chronic diseases over many years, early and specific diagnosis for the majority of patients needs to become a reality in order to react timely, with high therapeutic efficiency and ideally the lowest societal burden. The most promising approaches in achieving this in the near future comprise:

- Shift from reactive disease to health-centred care
- Early, repeated, and systems-oriented interventions (life style, combinations of drugs and environmental agents)
- Complex, kinetic intervention support systems developed by health care, academic research and pharma

One of the main reasons why we have still not reached these goals are the complexity of common diseases, which is further underlined by the huge amount of data being provided by state of the art biomedical analytical tools such as the –omics approaches. These have now reached the clinic in several fields and applications and whilst adding to the complexity of accessible data, they have substantially contributed to several major advances. One novel approach employing -omics data in a (pre-)clinical setting is the concept of network modules, which helps to understand disease mechanisms, find biomarkers and therapeutic targets. The concept has been used in a pioneering study to identify a new candidate gene in allergy as a novel clinical target. The outcome of this study is exemplary for many similar studies in the realm of Systems Medicine:

- A truly multi- and interdisciplinary research team led by a clinician worked concertedly in a joint project on a daily basis.
- Integration of -omics, bioinformatics, functional and clinical studies.
- Funding through public money with reasonable costs of 1-2 Mio EUR.
- Several partially high-impact publications, but clinical implementation failed within the scope of the project.

Conclusion

What does work: the integration of omics and clinical phenotyping with a strong IT approach, reconstructing networks and network modules, leads to predictive biomarkers and new targets.

What does not work: successful clinical implementation! It is barely feasible with current public funding schemes and timelines to translate results into the clinic as it requires GCP standard clinical studies of thousands of patients in many centres for many years entailing complex administration and regulation. Such activities can only be financed with a strong industrial partner, willing to invest and hence to take a major risk.

Recommendation

In order to make clinical implementation a reality in the future, several suggestions for upcoming funding initiatives can be made:

- Fund multiple, diverse projects aiming at patentable early and individualised diagnostics (success indicator).
- Allow Pharma to continue with implementation studies, in collaboration with basic and clinical researchers.
- Make clinical feasibility an evaluation criterion.
- Clinical leadership of projects increases feasibility of clinical implementation.
- Inclusion of clinicians with Systems Medicine experience in evaluation panels.

Discussion

Clinical implementation and tackling of complexity

- For some diseases, simple inexpensive tests might soon help to stratify patients and enhance therapy efficiency, whereas there is still a long way to go for other, more complex diseases. Severe diseases with costly therapies constitute the obvious low-hanging fruits in the quest for new, individualised diagnostic approaches with potential for rapid clinical implementation.
- The need to protect intellectual property from publicly funded research projects in Systems Medicine has already been largely acknowledged by the funding agencies. However, many research projects are still located at the very early stage of the innovation pipeline so that later implementation of results, even if protected, is often elusive.
- The use of computational tools to guide diagnosis and treatment is as well seen as a realistic means of translating Systems Medicine approaches into the clinic.

Lack of clinician scientists

- The apparent lack of clinicians active in life science research is one of the major hurdles to fostering implementation of clinically focussed research and implementation of research results in the clinic. This is evidently due to the current framework of clinical and research positions in Europe, which make it unattractive for clinicians to engage in research. The existing strong cultural gap between the clinical and the scientific world needs to be overcome in order to raise acceptance and interest for clinical scientist careers.
- A stronger and more proactive approach in including for example hospitals and clinicians in existing funding schemes such as the IMI or ERC research grants could aid in these efforts. Supporting both the establishment of training programmes dedicated to clinicians as well as the implantation of a framework for attractive clinical scientist positions will be a major task also for the funding agencies in the next years.

Systems Medicine in Europe – where do we stand?

Werner Müller, Bill Ford Chair in Cellular Immunology, University of Manchester, UK

Coordinator SysMedIBD

Presentation abstract

In recent years, several very promising interdisciplinary projects either focussing on or centrally containing Systems Medicine aspects have been initiated. Such projects range from developing assistance in autonomous living of senior citizens (inCasa), to exploring the genetic and non-genetic determinants for developing age-related macular degeneration (EYE-RISK), epigenetic-based prediction of therapy resistance in breast cancer (EpiPredict), and to new approaches in combinatorial therapy and biomarkers for Multiple Sklerosis (CombiMS).

The SysMedIBD projects fits well in that line as its multidisciplinary consortium strives to unravelling the disease-mechanisms of chronic inflammatory bowel disease (IBD) and to find new approaches for therapy through the use and integration of patient data, animal and computational models. The involvement of two SMEs, Lifeglimmer and GeneXplain, has substantially aided in employing pathway analysis of IBD to screen *in silico* for potential small molecule therapeutics as a first means to tackle clinical implementation. Within SysMedIBD, data from animal models have been used as a basis for computational models, which have been fitted to data derived from patient samples and from automatically digitalised patient records. These digital patient data proved to be a central knowledge repository in which data from all patients from a respective hospital are accessible, similarly to a well-organised retrospective cohort. Such “hospital cohort” information has the potential to be the basis also for predictive models with regards to the risk and progression of diseases.

Conclusion

The systemic approach in all of these studies is of central importance to tackle the complexity of model and patient data. Only with Systems Medicine approaches it is possible to go beyond the approach of evidence-based medicine: where evidenced-based medicine describes only the superiority of one treatment to the other, Systems Medicine provides an understanding of the reasons for the observation and can make predictions. Systems Medicine can take into account the interconnectivity of different conditions and diseases and focuses on the questions of disease progression and outcome, which will aid in the implementation of a more patient/person-based participatory and preventive medicine.

Recommendation

- Systems Medicine starts before the clinic: animal models are an important building block for Systems Medicine. Especially the gene to phenotype relation is important. Data needs to be collected systematically and be made accessible.
- Do not neglect basic research: while it is important to bring knowledge to the clinic, it is also important to enrich the knowledge base the knowledge base in the first place to provide understanding for networks and mechanisms.
- Patient data is quintessential: retrospective data from patient records is an important key for classifying patients. Digitalisation of patient records is therefore an important action to be supported. For prospective data gathering the use of mobile devices will give more accurate and time-resolved data than previously possible.

Discussion

Next steps in integration of data

It was discussed what will be the right next steps after digitalisation of patient data and initial integration with –omics data. Clearly, clustering of patients based on clinical data and then analysing similarities in their molecular make-up is a promising approach to generate new hypothesis and leads for understanding diseases.

Disease focus versus mechanisms / molecular hallmarks of diseases

It was further pointed out that on a molecular level, there appear to be certain invariant network components, which play a role in very different seemingly unrelated diseases and which have a high potential to lead to new therapeutic approaches in the mid-term future.

This common aspect of different diseases emphasises the need of having a scientific community based joint effort to develop common tools and generate decisive data independent of diseases. Cancer research as a pioneering discipline in Systems Medicine has meanwhile yielded a lot of molecular hallmarks for this disease (e.g. energy metabolism, inflammation). Other chronic diseases seem to share some of these hallmarks. It would be an important next step to follow-up on these also with regards to the increased prevalence of co-morbidities, whose occurrence might be based on shared hallmarks.

Therefore it is recommended that funding of systems medicine does also focus on the better understanding of the molecular hallmarks across different diseases.

LONGITUDINAL COHORTS – A TOOL FOR SYSTEMS MEDICINE

Regina Becker, Luxembourg Centre for Systems Biomedicine, LU

Presentation abstract

Longitudinal cohorts can provide the dimension of time to Systems Medicine studies by following people and patients over extended periods. Observing changes over time in a cohort of people can be critical to understand basic aspects of disease risk, disease progression, and disease influencing factors. Different kinds of longitudinal cohorts with varying scope exist:

Population cohorts observe a cross-section of the population over time and usually allow inferring the influence of life style-related aspects on health status.

Similarly, **birth cohorts** follow cohorts of individuals from their time of birth on, often including the mothers during pregnancy, and usually focus specifically on the influence of life style factors on the development of children or development of diseases later in life. Such studies will specifically help to further develop the field of epigenomics, as the epigenetic make-up appears to exhibit a high plasticity in early years.

Family studies help to understand heritability of complex diseases. Due to the high similarity of the genetic background and life-style of e.g. siblings, influence of single genetic mutations can be better attributed to phenotypes than in other cohorts.

Likewise, **twin studies** focus on related subjects, both on heterozygote and monozygote twins to pinpoint environmental versus genetic influences on health and disease.

Disease control cohorts focus on patients of a given disease or group of diseases compared to healthy individuals as control group. Such studies help to understand disease progression and co-morbidities, which develop alongside the main disease.

Risk cohorts follow a group of people, with a higher risk of developing a given disease such as genetically predisposed persons, persons showing prodromal symptoms, or persons having been exposed to known risk factors. Such cohorts allow to get a deep insight into early disease development and progressions and to identify prognostic markers as well as to evaluate existing predictive parameters and hence can serve well as “validation cohorts” for predictions derived from disease models.

Electronic health records could become the means of the de facto inclusion of almost a complete national population into a cohort. They allow direct computational analysis and are linked distinctively to individuals. However, comparability of data from these records will be limited since there is usually no standardisation, no quality control, and not central repository of biospecimens. In a few countries e-health records have already helped to generate new biomedical knowledge.

Modern technologies could help to raise the quality of data both generated in dedicated cohorts as well as in national e-health record databases. Wearable sensors and mobile devices already help to gather data continuously. Whole genome sequencing in in-depth –omics analysis further contribute to acquire additional and more significant data. The “Michel-Snyder-Experiment”, where a researcher has deeply analysed his own –omics profile over two years, gives a glimpse at the possibilities of personalised molecular analysis of single individuals.

However, any longitudinal cohort's quality can be distorted by unobserved confounding factors: the basis of selection for recruitment can bias a cohort's composition, regional recruitment can hamper the universal validity of results due to environmental, socio-economic, or gene pool influences. Likewise, a good quality and substantial extent of data as well as a standardised quality of sample collection and a critical mass of participating individuals are essential for the impact of any cohort. These aspects are often hampered due to lack of dedicated funding and weak retention of cohort participants.

Enrichment of existing cohorts by inclusion of further bio specimen collection or questionnaires as well as pooling of existing cohorts can help to raise the overall quality of cohort studies or the breadth of data basis in order to prevent low impact or poor result outcome. The JPND Action Group has published an excellent report on longitudinal studies, which can be downloaded here.

The mining of existing cohort data by the research community could clearly raise the overall knowledge gained from such studies. However, so far, few cohort studies freely publish original data sets and differing national ethical and data protection policies hamper free exchange of data. This pitfall has been acknowledged by the EC and specific Horizon 2020 calls have been issued to tackle optimisation of use of population and patient cohorts in the EU. Such efforts will also need to address the poor standardisation of electronic data records, which is already identified as a major drawback for harvesting of actually existing wealth of biomedical data.

Conclusion

(Longitudinal) cohorts have provided a better understanding of diseases and have the potential to make further contribution once they are made available for Systems Medicine. The use of omics data and the tools of Systems Medicine can bring the knowledge derived from cohorts to a new level.

The computational modelling in Systems Medicine specifically benefits from longitudinal data as the dynamic information gives better access to unravelling the complex networks. Cohorts also allow analysis of data retrospectively and predictions from models can be validated with prospective data.

As always in systems medicine: the quality of data and use of standards is key for the value of the cohorts.

Recommendation

- Funders should make sure that longitudinal cohorts in their country have reliable support.
- To increase the value and utilise previous investments, existing cohorts should be enriched through pooling of different cohorts, inclusion of additional subjects, molecular phenotyping and the inclusion of electronic health records and data from mobile devices.
- The access to the cohort data needs to be a prerequisite for funding to maximise the output.

Discussion

Value of longitudinal cohorts

It was agreed that longitudinal cohorts and data derived thereof are and will be absolutely essential for translational and clinically relevant research. Existing efforts such as BBMRI and national nodes need to be further supported in the sense of infrastructures rather than single projects. It will be important to strategically plan and implement future cohorts in order to be able to address pressing medical questions and to avoid fragmentation of the landscape. It was pointed out that although many funding agencies already require results to be freely published from supported cohort projects, the provision of access to original data would be desired and essential to realise the full impact such data can have in translational research.

Sharing of data from cohorts

Data sharing of cohorts needs to be strongly promoted for full leverage of the wealth of existing data. Europe's diversity in legislation poses a serious challenge for free scientific data exchange. Several EU-funded platforms and best practices exist e.g. within the framework of the IMI that should be employed more efficiently and by a broader scientific community. The direct association of established biobanks to cohorts should be encouraged as this usually facilitates inclusion of quality standards and data exchange policies. Again, overarching infrastructures such as BBMRI will be crucial in supporting single cohort studies to provide their data to the research community.

DENOPA – EXPERIENCES FROM RUNNING A LONGITUDINAL COHORT

Brit Mollenhauer, Paracelsus-Elena-Klinik Kassel, DE, Coordinator De Novo Parkinson (DeNoPa) cohort study via videolink

Presentation abstract

Brit Mollenhauer started her presentation with a brief introduction into the topic of Parkinson's disease (PD), which affects approximately 400-500.000 persons in Germany alone and has its peak incidence in the age of 60 to 64. Still, the underlying cause for PD is unknown and due to typically late clinical diagnosis, most patients are diagnosed at an advanced stage of the disease with already a high loss of dopaminergic neurons, one of the hallmarks of PD. In order to overcome the lack of understanding of the disease and learn about disease progression in different patients to potentially find new approaches for early diagnosis and therapy, longitudinal cohorts with subjects affected with PD are strongly needed.

The *De Novo* Parkinson's Disease (DeNoPa) cohort is specifically dedicated to early stage PD patients that have ideally not yet received any medication at the entry into the study. Brit Mollenhauer presents an extensive overview of questions and check-points that had to be clarified in the first place to demonstrate the efforts and challenges the setting up of a meaningful cohort entails. As a single centre cohort, DeNoPa started with 159 *de novo* PD patients and 110 healthy controls at the baseline analysis. In order to keep the retention rate on a level as high as 94-95% substantial amounts of energy and time are spent for dissemination and communication with the cohort participants through regular newsletters, the DeNoPa homepage, and regular retention meetings.

With the 48 months follow-up examination having recently ended, analysis results from the previous examination round were already shared. First potential new markers for PD progression based on scales and questionnaires of non-motor symptoms, REM-sleep behaviour disorder, and MRI volumetry could be identified. For further validation of the cohort's results, DeNoPa is teaming with the greater Parkinson's Progression Markers Initiative (PPMI), which is a multi-centre PD cohort funded by the Michael J. Fox foundation.

INTERNATIONAL ACTIVITIES IN SYSTEMS MEDICINE

Rudi Balling, Luxembourg Centre for Systems Biomedicine, LU, Coordinator SysMedPD

Presentation abstract

To date, only few dedicated Systems Medicine programmes have been launched worldwide. However, there are international initiatives beyond the known EU activities such as IMI or ERACoSysMed, which exhibit substantial overlap with Systems Medicine or deal with related topics. These include:

- The NIH Precision Medicine Initiative (US)
- The NIH Big Data to Knowledge (BD2K) Initiative (US)
- China Precision Medicine Initiative
- The 100k UK Genome Project
- The Estonian Personalised Medicine Programme
- Initiatives from the private sector

The NIH Precision Medicine Initiative is dealing with complex diseases with a focus on cancer and will include a cohort of 1 million persons, part of which is supposed to undergo molecular phenotyping and whole genome sequencing. This longitudinal cohort will integrate existing cohorts and *de novo* enrolment of participants over a set-up period of 3-4 years. Main objectives are identification of risk factors, developmental of predictive markers, new disease and drug response classifications, as well as novel mobile health technologies.

The BD2K Initiative complements the Precision Medicine by developing tools for big data management in biomedicine. It focuses on four main areas, namely (i) improving the ability to locate, access, share, and use biomedical big data; (ii) developing and disseminating data analysis methods and software; (iii) enhancing training in biomedical big data and data science; and (iv) establishing centres of excellence in data science, which will serve to implement the above aspects within the scientific community.

The China Precision Medicine Initiative will only be launched later in 2016. The expected budget appears to outpace the NIH Precision Medicine Initiative by far, yet China is struggling with scarcity of medical doctors and pathologists, which could hamper the implementation of the project.

The 100k UK Genome Project is supposed to connect the sequencing data of 100k human genomes with data available from the National Health Service. In the UK, the programme is seen as an important step towards personalised medicine, as the means to bring the technology of genome sequencing into national health care practice as well as building a strong UK genomics industry. However, the value of the programme, which strongly focuses on genome sequencing alone and but so far lacks a stronger computational and modelling component, remains to be seen.

The Estonian Personalised Medicine Program combines a 50k person longitudinal cohort with the national e-health infrastructure X-road, which comprises electronic health records and comprehensive registries. With the set-up of the national health information systems in 2008, Estonia has laid an important foundation for a data-driven health care system and industry and could become a leading role model for other countries in this regard.

Industrial companies like Google and Apple have recognised the potential of employing big data analysis for generating biomedical knowledge. Apple is focussing on the use of the iPhone as a hardware tool for daily routine use analysis, whereas Google is actively developing cloud-based health information services, search engines for genomic data, and deep learning methods. Further companies are active in the consumer health market indicating an increased awareness of future market potential in the field.

Conclusion

Common activities in the international initiatives are:

- Building of large longitudinal cohorts
- Focus on whole genome sequencing
- Integration of genomics data with medical records
- Collaboration with industry partners.

Smart elements in the initiatives are:

- The link of large-scale data generated to computational programmes
- The integration of mobile devices
- The direct integration of the healthcare sector
- The building on scientific consultation
- The support of industry in the country.

Recommendation

- Major efforts will have to be put into the aspects of standardisation and quality of data as well as the integration and scalability of data handling approaches.
- Importantly, the aspect of computational modelling based on the acquired and generated data must not be neglected in order to harvest the full potential of data in the sense of meaningful interpretation and prediction.
- It is strongly recommended to include research on the “Exposome” by integrating environmental and social sciences, which might prove to be key in unravelling the gene-environment interaction of complex diseases.

Discussion

Industry in Systems Medicine

From the perspective of public research, the industrial engagement poses the question, if industry players such as Google will be potential partners for academic research or rather competitors in dominating the market for developing and employing data driven health predications and excluding academic players in Systems Medicine. Different opinions were voiced regarding the question if industrial companies are already leading in the field. The lack of commercial successes so far may be an indicator that industry is equally challenged as public research. In addition, industrial research is driven by commercial denominators rather than gain of knowledge. Therefore, the benefit for society as a whole from industrial competitors was doubted by several participants. Additional doubt was expressed about the validity of current health recommendations based on mobile devices / internet portals due to a lack of validation of systems based on clinical data.

Collaboration with PerMed

It was pointed out and further discussed that the PerMed initiative is discussing similar topics with comparable discussion outputs such as the need in coordinating national efforts for true implementation of Systems and/or personalised Medicine. Although the Systems Medicine community is more scientifically driven and the personalised medicine community focuses stronger on the clinical

output, a substantial amount of challenges is actually shared and it is well agreed that Systems Medicine provides the tools that are a necessary precondition to make personalised medicine a reality one day. Therefore, the CASyM initiative and in the future the EASyM association is actively teaming up with e.g. the PerMed consortium and to work out joint future activities to support the necessary changes together.

ERACOSYSMED – LESSONS LEARNT AND NEXT STEPS

Sylvia Krobitsch, Projektträger Jülich, DE, Coordinator ERACoSysMed and

Carme de Andres Sanchis, Instituto de Salud Carlos III, ES, ERACoSysMed (JTC-2 Secretariat)

Presentation abstract

The ERA-Net Co-fund for Systems Medicine (ERACoSysMed) consortium of 14 funding organizations from 13 different countries supported by the European Commission was established beginning of 2015. Like CASyM, ERACoSysMed focuses on enhancing the implementation of Systems Biology approaches in both clinical research and medical practice. 3 joint transnational calls (JTC) are foreseen during the run-time of the ERA-Net co-fund. The first JTC (JTC-1) had been launched in February 2015 and included one third co-funding from the European Commission. The next two JTCs are to be launched in the beginning of 2017 and 2019, respectively, without EC contribution to the research projects funding.

The main rationale for the drafting of the JTC-1 call was to demonstrate the feasibility, benefits and potential of the Systems Medicine approach since these aspects are seen as instrumental for the initial step of the implementation process. Hence, JTC-1 was focussing on proof of concept and demonstrator projects.

The feasibility of a Systems Medicine approach were expected to be demonstrated in the proposals and supported by the excellence and interdisciplinary track record of the proposed partners. 9 projects were finally recommended for funding with a total requested budget of approx.12,7 million EUR. Scientific/clinical fields that are being addressed through the funded projects include (i) cancer, (ii) chronic diseases (Primary sclerosing cholangitis; asthma; ulcerative colitis), (iii) neurological diseases (multiple sclerosis), and (iv) cardiovascular diseases (cardiac resynchronisation therapy).

Conclusions

Lessons learned from JTC-1 for the following calls include that a two-stage review process including rebuttal phase as in JTC-1 is quite lengthy and may be exchanged for a one-stage process in JTC-2 (subject to the decision of the Call Steering Committee and to be confirmed in the coming months). Furthermore, hands-on experience has been acquired regarding the structure of the application template and handling of the online submission tool, which will be accordingly adapted for the following calls. A better gender balance within the reviewer panels should be striven for, as there was an evident lack of female panellists in JTC-1. A weak participation of SMEs in JTC-1 was noted, which is most likely based on limiting funding possibilities through the national funding bodies in many countries.

Most of the proposals exhibited weaknesses in data management and computational modelling approaches. Many proposed projects also lacked clinical data. The importance of data management and modelling concepts as well as the use of clinical or cohort data will thus be emphasised in future calls and a generally well-balanced representation of disciplines will be sought.

Next steps ERACoSysMed

- The preparation of the upcoming JTC-2 is currently underway. During the next ERACoSysMed meeting in April 2016 (Slovakia), the consortium partners will discuss potential call topics and procedures.

- A non-disease specific call could be envisaged. However, essential elements will be the clinical relevance as well as data management, modelling, and data integration. The inclusion of patient organisations or their representatives in each application is discussed.
- In November 2016, the JTC-2 pre-announcement is foreseen with a submission deadline in February 2017. A final funding decision is supposed to be given end of September 2017, reflecting the abridged review procedure. Projects can finally start operations in January 2018 (timeline to be confirmed in the coming months).

Discussion

Implementation of systems medicine

The potential role of ERACoSysMed in funding implementation projects for Systems Medicine was discussed. Computational models appear to be one of the most promising aspects of Systems Medicine approaches, where they provide the basis for clinical (decision) support systems. It was discussed though that the systems element in clinical achievements may not be visible. As an example, it was suggested that modelling of molecular networks and prediction of mechanisms can lead to new targets. However, once drugs are successfully developed for the targets, the role of Systems Medicine in their discovery may not be acknowledged. Therefore it is important to consider also systems medicine as an important element in fundamental research. It is necessary to support systems medicine in all stages of research and keep track of the success parameters in all parts of the developmental chain to communicate the relevance of it for the overall success in new treatments. An awareness of the full scope of Systems Medicine is needed and a major activity is necessaryto increase Systems Medicine visibility.

Potential topics of JTC-2

The current plans for JTC-2 do not yet contain a clear list of potential topics or conditions to be addressed.

Based on the previous discussions, it was emphasised that “analysing pathways across diseases” could prove to be a very promising topic both in terms of attracting high level project partners as well as potential high-impact outcome. Similarly, energy metabolism and inflammation as a potential driver of complex diseases were discussed as highly promising potential topics.

Set-up of the projects: consortium composition and project duration

The low participation of SMEs in the first call was discussed. It was concluded that Systems Medicine is not yet of prime interest for small companies. In addition, it was not possible in all countries to fund companies from the national budgets.

There were considerations if consortia should have more than one clinical partner to ensure sufficient patients. It was decided though that this might depend on the disease fields as well as on the clinical partner. Therefore number of partners in the different domains should not be pre-defined in the call but left to the evaluators to assess the adequateness.

Many projects need a longer time than the usual 3 years duration for results with clinical impact. The feasibility of a longer funding was discussed with a potential cut-off after 2 years.

UPDATE ON PRIVATE FOUNDATIONS AS PLAYER IN INTERNATIONAL INITIATIVES

Regina Becker, Luxembourg Centre for Systems Biomedicine, LU

Presentation abstract

Since the initial presentation on the role of private foundations in international funding initiatives during the last funders' meeting in 2014, further explorations have been made by the CASyM Work Package 5 members. Additional foundations have been contacted and the full report of the EU-funded EUFORI[1] study on its analysis of European foundations active in supporting research and innovation was studied.

All over Europe, foundations have contributed more than 5 billion EUR on research, 63% of which with medical relevance and 44% of surveyed foundations welcomed European collaboration. The EUFORI study analysed more than 1500 foundation all over Europe. It was observed that there are strong regional differences in the contribution of foundations to the overall research budget. The distribution is highly skewed with 4 countries being responsible for more than 66% and 1% of foundations providing 50% of total research spending. Despite the openness for European collaboration, so far only 10% of all foundations operate on an international level, which results from cultural, legal, and fiscal barriers. The UK, Germany, Denmark, and Sweden rank first in the list of high R&I spending from foundations whereas substantially lower amounts were reported from Eastern Europe and smaller countries.

A principal difference in operation and positioning within the foundations landscape depends on the modus operandi of foundations: grant-making foundations fund research activities outside their foundations by granting monetary aids (e.g. Arthritis Research UK), whereas operating foundations fund research performed within their on institutes and premises (e.g. Institut Pasteur). A strong correlation suggests that most grant-making foundations receive their income from endowments while operational foundations are often grant-seekers. For the interest of CASyM therefore, the grant-making foundations with income from endowment and high spending budgets are the most interesting candidates to join the national funders in their efforts. Looking at the corresponding foundation landscape, it can again be observed that operating foundations are predominantly found in smaller and Eastern European countries; there is a striking combination of a high number of grant-giving foundations, significant spending budgets and income from endowment in the Nordic countries as well as the UK. In general, there is a decline from north to south and from west to east.

The CASyM work package 5 survey has by now contacted 38 foundations in 11 countries. Only major stakeholders in project funding with annual funding budgets of over 3 million EUR in health research have been selected and contacted for structured phone interviews.

Conclusion

The results the CASyM survey of foundations generally match the EUFORI study results: potential funding partners have been identified in the Nordic countries and the UK as well as some in France and in Germany, whereas no partners could be identified in Eastern Europe and smaller countries such as Austria and Ireland.

Interest on a potential participation in an ERA-Net consortium was only demonstrated by disease foundations. However, countries like Germany and France also showed a general reluctance to give

[1] www.euforistudy.eu

up control in a consortium of funders. In addition, the administrative burden for the active participation in ERA-Nets were named as a major obstacle to decide for a participation.

Constructive feedback on the necessary preconditions for collaboration in an ERA-Net consortium has been given by some foundations interested in collaboration: ensuring a high quality of the review process and participation in the final decision on selection of projects was mentioned as important aspects to decide on participation. At the same time, some foundations indicated willingness to fund cross-border and uttered a specific interest in Systems Medicine. Participation could be envisaged at different stages of a call ranging from active participation in the phrasing of the call to inclusion at the level of selected projects.

Recommendation

The following recommendations for the inclusion of foundations into ERA-Nets can be given based on the overall feedback from contacted foundations and the analysis of the EUFORI report:

- Inclusion of interested foundations from UK, Netherlands, & Norway
- Exploration of the interest of foundations in Denmark, Sweden, Norway, & Finland
- Build equal partnerships by involving foundations early on and bottom up
- Explore cross-border funding and possibilities for flexible funds through foundations
- Keep administration at a minimum
- Participation in common calls may ease „rescue funding“ in others

Discussion

Potential involvement of foundations in ERACoSysMed

The representatives of ERACoSysMed showed a strong interest in the details of the survey and the contact details of the interested foundations. Positive experience with the inclusion of private foundations in previous ERA-Nets such as TRANSCAN and E-Rare was mentioned by various funders.

The possibility to be able to potentially fund research consortia with partners in countries that are not members of ERACoSysMed (e.g. UK) was seen as an especially interesting option in including private foundations. It was concluded that it would be advisable to actively inform disease foundations of the results of the first ERACoSysMed call to raise their interest. There might even be interest for participation in the disease-open calls due to the focus of projects on clinical impact.

UPDATE ON CASyM

Charles Auffray, European Institutes for Systems Biology and Medicine, FR, CASyM steering committee

Presentation abstract

Charles Auffray gave a comprehensive overview over the CASyM Coordination Action: 22 partners from 11 countries and meanwhile more than 100 associated partners had teamed up to formulate a European-wide implementation strategy for Systems Medicine with a clear focus on clinical needs.

Based on CASyM, there are currently three further activities supporting the implementation of Systems Medicine in Europe: the ERACoSysMed, the Systems Medicine Web Hub, as well as the European Association of Systems Medicine (EASyM). When the CASyM project will be finished, the EASyM will carry on the activities in the scientific community and ERACoSysMed in the funders' community.

The Systems Medicine Web-Hub is up and running for several months now. Its main purpose is the channelling of information in the field from various sources for the interested reader. The Web-Hub is well perceived in the community and will be constantly updated and further developed.

EASyM is founded as one of the central outcomes of CASyM to continue the role as community integrator. The society was founded on the 30th of September 2015 and has its headquarters in Aachen, Germany. As an independent legal entity, EASyM can sign agreements with partners and can hence play an active role in the promotion of Systems Medicine. EASyM is currently focussing on organising its annual conference and on promoting Systems Medicine publications. The first EASyM annual conference will take place from the 26th until the 28th of October 2016 in Berlin. Topics will include:

- Overcoming patients drug resistance
- Making sense of Big Data in healthcare
- Patient involvement in the era of personalised medicine
- Tackling inflammation in chronic and infectious diseases via Systems Medicine

In the future, further activities are envisaged. Goals are the increase of EU-funded partnerships and proposal success rates, stronger support of clinical research projects, and a continuity of contact between the Systems Medicine research community to the European Commission. EASyM is striving to support the implementation of Systems Medicine projects focused on complex biological processes to tackle unmet clinical needs by employing European biobanks, computational and data management infrastructures and public-private partnerships (BBMRI, EATRIS, ECRIN, ELIXIR, CORBEL, IMI-2, EIT-Health etc.). It is EASyM's objective to federate multiple initiatives (CASyM, PerMed, Avicenna, EAPM, ISBE etc.) to form a coordinated opinion and have a higher impact both in Europe and on the international scene.

Discussion

Concerted Action

It was largely acknowledged that Systems Medicine has reached a certain maturity. Already during the run-time of the CASyM project, a leap could be observed from a scarcity of Systems Medicine projects, let alone successful clinical implementation, to a variety of promising demonstrator projects and success stories. It was agreed that there seems a promising future of new discoveries if an increased standardisation can be achieved, if cohorts are being utilised to their fullest, and *in silico* models can be derived on such improved data. Concerted actions on a European level are important

and the need to work hand in hand to overcome fragmentation was acknowledged. ERACoSysMed and also PerMed are seen as first steps in the right direction. Future activities will depend on the success of these initiatives.

ACKNOWLEDGEMENTS

This document is part of CASyM work package 5 – “Integration of national efforts in Systems Medicine and within the EU”.

CASyM is funded by the European Union, Seventh Framework Programme under the Health Cooperation Theme and Grant Agreement # 305033.

Steering Committee - The following officials, as part of the Scientific Steering Committee, are involved in the scientific coordination of CASyM:

Charles Auffray - European Institute for Systems Biology & Medicine - EISBM, France
Mikael Benson (Deputy Speaker) - Linköping University Hospital, Sweden
Rob Diemel - The Netherlands Organisation for Health Research and Development, The Netherlands
David Harrison (Speaker) - University of St. Andrews, United Kingdom
Walter Kolch - University College Dublin, Ireland
Johannes Mohr - Federal Ministry of Education and Research, Germany
Francis Lévi - Institut National de la Sante et de la Recherche Medicale, France
Damjana Rozman (Deputy Speaker) - University of Ljubljana, Faculty of Medicine, Slovenia
Johannes Schuchhardt - MicroDiscovery GmbH, Germany
Olaf Wolkenhauer - Dept. of Systems Biology & Bioinformatics University of Rostock, Germany

Administrative Office (Coordination)

Marc Kirschner - Project Management Jülich, Forschungszentrum Jülich GmbH, Germany

□


CASYM
EUROPE
SEVENTH FRAMEWORK
PROGRAMME