Future Organization of Clinical Research in Germany: The Road to the „German Centre for Digestive Health“ (GCDH)

Author: Michael P. Manns, MD, Professor of Medicine, Director Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School (MHH), Clinical Director Helmholtz Centre for Infection Research (HZI, Braunschweig)

E-Mail: manns.michael@mh-hannover.de

Homepage: www.mh-hannover.de/gastro.html

1. Unmet needs have to be defined

Despite of all the freedom necessary for independent research “unmet needs” in clinical research have to be defined based on problems arising from everyday patient care. Politics in general and research politics in particular have to decide how much tax payer money should or can be allocated to overall research and to biomedical research in particular which also means investment in the future of the society. Demographic changes all over Europe force governments as well as the whole society to change strategies. However, the definition of specific topics to be tackled by national and international research programmes must be defined by the scientific community. The German Ministry of Research and Education (BMBF) has continuously reached out to the scientific community including scientists in clinical medicine. Approximately one decade ago the road map concept was designed by the BMBF ministry in close collaboration with basic and clinical scientists. Research funding is not only based on tax payers’ money but also on private investment and donations including support by private foundations and the pharmaceutical industry. In Germany universities are run and financed by the individual 16 states of the federal republic. In addition the Federal Government (Bundesregierung) supports academic research in various ways. One major source of university research funding is through the German Research Foundation (Deutsche Forschungsgemeinschaft - DFG). The German Research Foundation is an association where all the individual universities are individual members. This is described in German as “Vereinsmodell”. Further federal government research funding is mediated through specifically defined programmes of the Federal Ministry for Research and Education (BMBF). BMBF funded programs are usually designed for a limited time period. The Federal Government also finances non-university research institutes which on average are partially financed by the specific states where they are located. There are several non-university research organizations with individual research institutes all over Germany. These include institutes of the Max-Planck Society, the Leibniz Society, the Association of Fraunhofer Institutes and the Helmholtz Association of Research Institutes with its five institutes focused on biomedical research (www.helmholtz.de). The five Helmholtz Institutes for biomedical research are also playing a central role within the German Centres of Health Research (Deutsche Zentren der Gesundheitsforschung (DZGs)). These DZGs established an important national network between university and non-university translational and clinical research institutions.

Collaboration between university and non-university research institutions need to be explored and further developed in order to successfully tackle the biggest unmet needs in clinical research. For their translational research programmes non-university research institutions more than ever need access to patient cohorts and thus patient care. This is not possible without a close collaboration with academic medicine. In Germany academic hospitals are run by the university itself which differs from many other countries like England, USA and Australia. University hospitals have to strengthen and further develop their infrastructure for patient-oriented research. In addition to further develop and strengthen the institutional infrastructure paths for individual careers and chances have to be further developed that allow physicians with a research interest to develop a career in academia as a clinical scientist after completion of research as well as clinical training.

The establishment of various German Centres for Health Research (DZGs) has highlighted several major health burdens and threats to the society. Significant resources were allocated to these DZGs. DZGs were so far established for translational research in cancer, heart, lung and neurodegenerative diseases, infectious diseases as well as diabetes (www.bmbf.de/de/deutsche-zentren-der-gesundheitsforschung-394.html). In addition significant attention and funding has been allocated to the research in rare diseases: “Care for rare”. Years before DZGs were established and funded by BMBF “networks of competence” in medicine as well as integrated research and treatment centres (IFBs) were established and also funded with hundreds of millions of Euros (www.kompetenznetz-medizin.de; www.ifb-portal.de). All these major efforts by the BMBF aim at improving translational and clinical research in Germany. The field of gastroenterology and hepatology was quite successful in the programme of “networks of competence” in medicine through the establishment of the network of competence on viral hepatitis (HepNet) (www.kompetenznetz-hepatitis.de; www.deutsche-leberstiftung.de) and inflammatory bowel diseases (Kompetenznetz CED (www.kompetenznetz-ced.de)). However, gastroenterology and hepatology so far have been unsuccessful in acquiring resources to establish a specific DZG or IFB. Some members of our scientific community are involved in the German Centre of Infection Research (DZIF) (www.dzif.de). The field of gastroenterology and hepatology which is best described by “digestive health” covers a huge spectrum of acute and chronic diseases which are threats not only to the individual patient but also a major burden to the society and ideally coped with what the German language calls “Volkskrankheiten”. United European Gastroenterology (UEG (www.ueg.eu)) which is the umbrella of national societies of gastroenterology and hepatology, altogether 46 and the European scientific societies of all its subdisciplines (altogether 16) has published a white book (<https://ueg.eu/epaper/WhiteBook.Brochure/index.html>) under the title of “digestive health”. The term “digestive health” summarizes ideally much better what is covered by all the different aspects of our discipline than any German word could do. These diseases include chronic inflammatory gastrointestinal diseases like inflammatory bowel disease (IBD) and gastritis, acute and chronic pancreatitis, acute and chronic liver diseases including alcohol induced liver disease, fatty liver disease (metabolic), viral hepatitis A - E, chronic cholestatic liver diseases, gastrointestinal, pancreatic and liver cancer as well as nutrition medicine. This also includes disciplines in pediatrics as well as internal medicine and also the various disciplines of visceral and abdominal surgery.

2. Diseases nor research accept borders

More than ever clinical research has to be international. On the one hand diseases don't respect borders. On the other side problems in clinical medicine have to be tackled at an international level, in particular at the European level. Clinical trials and patient cohorts have to be conducted and recruited internationally. More and more research funding is competitively distributed at the European level through the European Commission, e.g. through the Horizon 2020 programme. Therefore it is a must that the scientific community, in particular the societies under the umbrella of UEG and the scientists behind it, actively contribute to the design of European Research Programmes. Some years ago the BioMed Alliance was founded (www.biomedeurope.org). The BioMed Alliance is an association of more than 25 individual scientific societies representing more than 250 scientists from all over Europe. The BioMed Alliance was primarily founded through the activities of cardiologists, oncologists and diabetologists. Nowadays among the 25 scientific organizations United European Gastroenterology (UEG) and the European Association for the Study of the Liver (EASL) are well established members. The present president of the Biomed Alliance Prof. Colm O'Morain (Dublin) is the previous president of UEG. Based on its activities and collaboration with members of the European Parliament (MEPs) successful efforts have been established to lobby for increasing research funding into biomedical research in Europe. This is necessary when we consider that 16% of all research funding in the United States goes into biomedical research projects while this is only true for 8% in European research funding. In particular the demographic changes seen in Europe demand for increased investments in biomedical research in Europe. So far Biomedical research receives much more attention and funding outside Europe, e.g. in the United States and some countries of Asia. Recently the European commission established the Scientific Panel for Health (SPH). The SPH consists of 27 scientists representing a wide range of disciplines and geographical areas and is particularly designed and entitled to advise the European Commission and here in particular the European Commissioner for Research and Innovation in biomedical research with a special emphasis on Horizon 2020, but also in developing and establishing future research programmes beyond Horizon 2020. The establishment of the Scientific Panel for Health on January 1, 2015, is a major achievement which would not have been possible without all the efforts by the BioMed Alliance. SPH is entitled to play a key role in the development of future research structures, institutions and programmes. One important vision for the future is also the establishment of a European Institute for Health Research in analogy to the National Institutes of Health (NIH) in Bethesda, USA.

3. Clinician Scientist Programmes have to be extended

No clinical research without patients! Therefore clinician scientists are needed which means physicians that take care of patients and run research projects. Maybe this cannot happen at the same time. However, clinician scientists should have completed both clinical postgraduate training as well as postgraduate research education. Education in research has to happen in specific programmes. These days in Germany the number of MD students performing an MD thesis is declining. Therefore at some universities structured MD/PhD programmes have been established. These are usually recruiting internationally and the language is English. The present generation "Y" asks for an acceptable work life balance that seems to differ from previous generations. New paths and new career chances have to be developed. Up to 70% of MD students nowadays are women. Applications for research fellowships funded by the Deutsche Forschungsgemeinschaft/German Research Foundation (DFG) to obtain postdoctoral training in particular abroad are declining. Therefore candidates willing to develop an academic career in medicine need to be identified, guided,

supported and followed. Of course working recharge has to be adequately rewarded and paid for. However, research and public service together with the German law named “Arbeitszeitgesetz” are difficult to combine or, as coined in the German language, rarely fit under one hat. Research and in particular clinical research is a mixture of sport and art. Successful will only be those who on the one hand are eager and ambitious and on the other hand are creative. A combination of both will lead to success not only in sport and art but also in research.

4. Cooperations between universities and non-university research institutes are crucial

As outlined above the possibilities of collaboration between research at universities and non-university institutions must be further developed both at the national and international, and there in particular European level. In addition the chances of collaboration with the pharmaceutical industry have to be further developed. The budgets of the large international pharmaceutical industries exceed a billion Euros or Dollars. Without any doubt the collaboration between academia in medicine and the pharmaceutical industry has to avoid and to make transparent conflicts in interest. However, the role of academic medicine for the development of therapeutic strategies and drugs has to be defined. Nevertheless drug development is not possible without academic medicine. For this intellectual property (IP) has to be secured for the universities and their scientists. Here universities have to increase their efforts to establish patents in order to secure rights once developments and inventions in academic medicine coming out of basic and translational research should be economically explored. Only if the rights are secured by safe patents pharmaceutical industries will license products and secure investments to develop these products and on the other hand pay license fees to universities and their scientists. At the later stage of drug development clinical development of drugs demands phase 1 to 3 studies. These should and have to be done at public institutions like hospitals and in particular university hospitals. Here I don't see any alternative. In particular the university hospitals have to develop an infrastructure and provide resources that allow clinical trials in phase 1, 2 and 3 studies. This includes statistics, biometry and clinical pharmacology. If the pharmaceutical industry is running hospitals themselves to conduct own clinical trials in their own institutions this cannot be regarded as the ideal path.

5. German Centre for Digestive Health – the biggest unmet need

The ambitious programme of the German Centres for Health Research (DZGs) funded by the Federal Government through its BMBF ministry aims at establishing virtual centres of translational research tackling all major disease threats in Germany. These DZGs form a network with a particular Helmholtz Institute in its centre partnering with on average 6 medical universities each with an expertise in the particular area. The decision for the establishment of a DZG was based on a peer-review process through international experts. Based on this international peer-review process DZGs were founded for oncology, neurodegenerative disorders, heart, diabetes, lung and infectious diseases (www.bmbf.de/de/deutsche-zentren-der-gesundheitsforschung-394.html). A major missing health burden not addressed by a German Centre for Health Research (DZG) is what gastroenterology and hepatology stands for. As outlined above this is described best by “digestive health”, much better than any German idiom could do. Without any doubt “digestive health” is covering a complex and heterogeneous area of medicine, much more heterogeneous for example than cardiology. “Digestive health” includes infectious diseases, several chronic inflammatory diseases of unknown cause, and

various tumors; altogether a major health burden for the society. Under the umbrella of “digestive health” there are such heterogeneous and challenging disorders like inflammatory bowel disease (IBD), gastritis, pancreatitis, viral hepatitis A - E and chronic liver diseases of unknown cause like primary biliary cholangitis or primary sclerosing cholangitis and most prevalent above all alcoholic and non-alcoholic fatty liver disease as well as gallstone disease. Gastrointestinal oncology is covering tumors of the oesophagus, stomach, colon, pancreas, liver and biliary tract that are the most prevalent solid tumors at all. While progress has been significant in many tumor diseases like colonic cancer there has been very limited progress in others like pancreatic cancer. The latter is one of the leading causes of cancer death worldwide apart from liver cancer. “Digestive health” also covers nutrition medicine with its strong link to obesity – a true epidemic threatening Europe, the Western world and beyond. Patients with obesity have an significantly increased risk to develop cancer; leading examples are colon, liver and pancreatic cancer. Twenty percent of Germans have some form of fatty liver disease. These patients have an increased risk of overall mortality not only liver related, in particular from cardiovascular disorders. “Digestive Health” also includes pediatric gastroenterology and hepatology with its genetic disorders. Many of these genetic diseases are now being treated successfully in childhood; as a consequence patients mature and advance to adulthood medicine with all its consequences. These genetic diseases include cystic fibrosis and inborn errors of metabolism for example of the liver. Liver transplantation has also been successfully established in childhood and patients grow up and live for decades. A new discipline in medicine has been created – transition medicine – taking care of patients growing out of pediatrics. However, structures are missing to take care of these patients in adulthood medicine. Under the umbrella of the German Society of Gastroenterology (Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS)) with related associations like the German Association for the Study of the Liver (GASL) it should be possible to convince politicians and public research organizations like the BMBF, DFG and non-university research institutions like the Helmholtz Society to establish a German Centre for Digestive Health (GCDH). This will close a significant gap in the network of the German Centres for Health Research (DZGs). A German Centre for Digestive Health would not only close an important gap in the DZGs but would also tackle one of the biggest unmet needs. The scientific and clinical strength of German scientific community of gastroenterology and hepatology should enable and facilitate the establishment a German Centre for Digestive Health “GCDH” as part of the DZG network. Hopefully this dream comes true in the not too far distant future.

Literature for further reading:

Deutsche Zentren der Gesundheitsforschung (www.bmbf.de/de/deutsche-zentren-der-gesundheitsforschung-394.html)

Kompetenznetze in der Medizin (www.kompetenznetze-medizin.de)

United European Gastroenterology (www.ueg.eu)

White Book der UEG (<https://ueg.eu/epaper/WhiteBook.Brochure/index.html>)

Scientific Panel for Health (<https://ec.europa.eu/programmes/horizon2020/en/h2020-section/scientific-panel-health-sph>)

BioMed alliance (www.biomedeuropa.org)

Deutsche Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (www.dgvs.de)