Bericht zur Öffentlichen Abschlussveranstaltung der Klausurwoche 01GP1482 Pluripotente Stammzellen: Lebenswissenschaftliche Praxis der Stammzellforschung und ihre ethische, soziale und legale Kommentierung

Panel Discussion at the Münchner Kompetenzzentrum Ethik at Ludwig-Maximilians-University Munich, April 27th 2017

Stem Cell Research. Regulatory and Ethical Challenges at the Threshold of Application

How could and should regulatory agencies worldwide react to the emerging clinical and commercial application of stem cells and the manifold problems and prospects brought about thereby? This year we count 19 years after the first successful cultivation of human embryonic stem cells and 11 years after the discovery of the reprogramming factors to generate so-called human induced pluripotent stem cells. The great promise that stem cell researchers' insights into human development and cell differentiation would soon be translated into cures for a wide range of diseases seems to come closer to fulfillment according to some. Many stem cell based clinical trials are underway, experimental medical treatments are being offered to patients, induced pluripotent stem cells are being used for disease models and pharmaceutical tests and a huge global market for unproven stem cell treatments has emerged. Other observers however remind us of the still enormous lack of scientific understanding of stem cell phenomena and warn that current commercial applications and clinical trials are for a large part ahead of evidence and might be premature. The panel discussion *Stem Cell Research. Regulatory and Ethical Challenges at the Threshold of Application* addressed the pertinent tensions between ethical, legal and practical demands. The event was organized by Arne Manzeschke and Anja Pichl from Institute TTN at the LMU Munich in cooperation with the Münchner Kompetenzzentrum Ethik at the LMU Munich, where it took place on April 27th from 5 – 8 pm. The panel discussion was the closing event of the international summer school *Pluripotent Stem Cells. Scientific Practice of Stem Cell Research: Ethical, Legal and Social Aspects and Discourses*, funded by the German Ministry of Education and Research (BMBF).

The following report will briefly outline the main idea behind the conference and additionally provide the summaries of the talks of three out of the four distinguished speakers written by themselves.

The topic

The much promoted progress of the global research community as well as market participants toward stem cell application gives rise to manifold regulatory and ethical challenges. There seems to be a widespread consensus that internationally harmonized regulations and implementations of standards are necessary and helpful in order to ensure scientific validity and good clinical practice of emerging stem cell treatments and to enable and ease international scientific collaboration. However, which are the right rules and standards and whether the official (by critics called ”hegemonic” or ”orthodox”) scheme of clinical translation is the best and only way to generate stem cell therapies gets increasingly contested. Europe largely follows a tightly controlled and thus rather slow pathway from bench to bedside which has not yet generated many approved treatments. Exceptions are blood stem cell treatments building on long established bone marrow transplantation. But elsewhere global markets of stem cell therapies flourish and offer treatments for nearly any kind of disease to people called “desperate patients” by some, “health consumers” by others. These treatments usually lack evidence of safety and efficacy. The standard passage from basic research via preclinical and clinical studies towards FDA/EMA approved treatments and their clinical application takes approx. 10-15 years full of uncertainties and is only then offered to all patients who often don't have alternative treatments. The

high costs, high technology and administrative capacities necessary for clinical trials are also criticized for disadvantaging academic institutions and smaller companies and excluding technologically and economically less well-developed regions from taking part in research and innovation. In many parts of the world, especially in Asia (but also in the US via hospital exemption and private clinics and especially the 21st Century Cures Act), alternative routes towards stem cell therapies have been established, sometimes conflicting with, sometimes adjusted to international standards and guidelines.

There is growing disagreement on how to shape, regulate and ethically evaluate the transition "from bench to bedside" in the best interest of patients, scientists, market participants, regulatory agencies and entire states promoting and protecting their national bioeconomy. Regulatory and scientific authorities especially in Western societies usually dismiss the development of the global stem cell therapy market without regulatory oversight and criticize what they perceive as exploitation of vulnerable patients and a threat to the good reputation of stem cell science. Many patients and patient organizations however seem to disagree with them about what risks they reasonably should take under their medical condition and advocate their "right to try".[1] This situation gets further complicated due to the fact that the adequacy of evidence criteria and methodological standards for stem cell therapy development and approval is contested not only among patients but also and especially within the medical and scientific community.

On the one hand there is a trend towards international harmonization and (Western) standardization aiming to ensure patient safety and scientific validity as well as competitive advantages via classic clinical translation. On the other hand there is a trend towards regulatory diversification aiming to enable faster and more cost-effective medical innovation and participation in the stem cell therapy market. These developments together with fundamental epistemological uncertainties and the nonetheless fast pace of scientific and market development make it very difficult to evaluate steps on the way from bench to bedside and design suitable regulatory frameworks. The concluding discussion after the four talks summarized below focused especially on the problematic lack of evidence for commercial stem cell treatments and even more worrisome lack of agreement about the right evidence criteria which were deemed crucial for evaluating steps into clinical and commercial application. As one major problem within current regulation of stem cell research has been identified the lack of differentiation between more risky cell types such as embryonic and induced pluripotent stem cells and more familiar and well-understood stem cells derived from bone marrow. The strict regulation was said to hinder the development of clinical application of the latter by overregulating their use – practical problems arising thereby where discussed in detail in the talk of Christine Hauskeller. A sharp contrast of the regulation of stem cell research to chirurgy was mentioned, where high-risk interventions are undertaken with nearly no regulatory oversight or prescriptions. The regional diversity of regulations however enables more restrictive regulations as people can seek treatments beyond boundaries – which poses social justice questions as these options are not available to everyone due to income restraints.

Anja Pichl

Summaries of the Talks written by the speakers

[1] Thi is even expressed by the International Society for Cell Therapy who states that patients and families „should have the right to seek treatment for their diseases. No entity should withhold that fundamental right unless there is a high probability of harm to the patient"

Translational research using induced pluripotent stem cells (IPSC): Between patients' expectations and ethical regulations

Zacharias Kohl

The generation of human induced pluripotent stem cells (iPSCs) from somatic cells obtained from adult donors provides new opportunities for stem cell based research, e.g. for neurodegenerative diseases. The Bavarian research network induced pluripotent stem cells (ForIPS) uses iPSC derived neural cells as specific cellular models to analyze the pathogenesis of Parkinson's disease (PD). Moreover, the consortium establishes a biobank for IPSCs and their derivates from PD patients and healthy controls. While the generation of iPSCs circumvents ethical limitations arising from the destruction of human embryos, several new issues emerge with the spread of iPSC technology: Here, informed consent to the generation, storage and distribution of iPSCs and their derivates are of high relevance. Further aspects are the potential tumorigenicity of iPSCs, or the production of germ cells from iPSCs. These ethical concerns face enormous hopes and expectations from patients with PD and related neurodegenerative diseases for the development on new therapeutic options.

The German Debate on Stem Cell Research

Klaus Tanner

[without abstract]

European Regulations and their effects on clinical trials

Christine Hauskeller

European regulation has been harmonised to create a unified platform that enables innovation in regenerative medicine. This regulation applies also to all new stem cell clinical trials. Findings from observing a phase III clinical trial indicate that it was unexpectedly difficult to conduct. Many problems arose directly and indirectly following the recent harmonisation of implementation rules to the EU Cells and Tissue Directive. Laws and regulations may be drawn up to protect patients and moral values, they also directly influence research and innovation pathways. By treating all new stem cell therapies the same, comparatively straight forward clinical trials with adult cells and led by clinicians become especially unfeasible. The harmonised regulation has undermined any meaningful connection between the stringency of regulations and controls and the clinical risks and complexity of any specific stem cell treatment. Stem cell research that is not geared toward industrial cell-based products and is not patentable becomes undoable, and that under the premise of making sure morally problematic and risky stem cell science is properly governed in Europe.

Balancing Social Justice and Risk Management in the Regulation of Clinical Stem Cell Research

Achim Rosemann

The regulation of the ways in which emerging fields of medicine are translated from the lab bench to the clinic and the market is at present in the midst of a global renegotiation process. Established ethical norms, clinical research methods, standards and the forms of evidence through which promissory medical approaches are tested and validated are increasingly contested and subjected to change. Stem cell medicine provides an important window to gain insights into these controversies, and into the

ways in which researchers, patients, corporations and regulatory authorities respond to these processes. One analytical dimension through which current forms of resistance and regulatory change in stem cell medicine and other emerging fields of medicine research can be explained is a concern with issues related to social justice. As I will show, at the heart of current conflicts on regulatory standards and evidence criteria is a tension between the management of technology risks and the realization of social justice, conceptualized not only in terms of access to new technology products and benefits, but also in terms of access to new innovation and market opportunities by researchers and technology producers. Indeed, the use of the language of social justice has evolved to an important political tool in a struggle for deregulation, the rejection of multi-phase trials and the promotion of "right-to-try" medicine. These calls for alternative standards and practices have important geographic dimensions. Resistance to the high costs of evidence-based medicine has emerged in particular in the context of low-to-middle income countries, but has become increasingly common also in high-income countries, such as Japan and the USA. The presentation explores these processes and also engages in a brief dialogue with existing academic explanations of regulatory diversification in the stem cell field, especially Sleeboom-Faulkner et al.'s notion of "national home-keeping" and Salter, Zhou and Datta's conceptions of "biomedical hegemony" and "biomedical adaptation". The presentation reveals that in light of the specific risks of stem cell medicine, very particular challenges for the realization and management of social justice claims emerge. This raises important questions with regard to the role, limits and the theorization of the social justice concept, not only in the governance of new medicines but also in other areas of technology research.