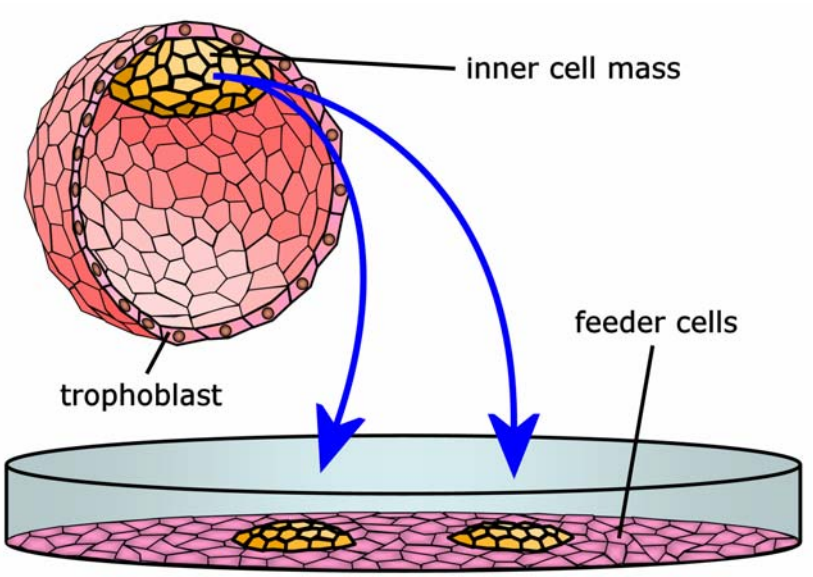
Proteome Biology of Stem Cells



a joint ISSRC and HUPO Initiative

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Contents

Proteome Biology of Stem Cells

Rationale of the initiative

Stem Cells

Stem cells form an area of biomedical research receiving broad attention in the scientific literature and the world media alike. This has been inspired by the notion that human embryonic stem cells have the unique property to form all cells in the human body, once they receive the proper signals. The control of this property in vitro would offer tremendous opportunities to develop treatments of diseases that cannot be cured today, especially in the area of regenerative medicine where the aim is to replace damaged tissue, particularly in organs where capacity for repair is inherently low (e.g. pancreas, heart, nervous system). The approach is of proven value in the clinic, in that hematopoietic stem cells offer curative options in a number of diseases. But there is requirement for other kinds of cell types for cellular therapies and there is a great deal of promise that these can be derived from human embryonic stem cells. Thus, intensive efforts are being put into multiple approaches aimed at developing stem cell therapies, from defining standardized culture conditions for expansion of stem cell lines, to designing and optimizing strategies for directed differentiation to specific cell lineages and, in the long term, finding ways to implant cells with the required properties in animals and humans without challenging the immune system. Apart from these clinically-orientated applications, there is great interest in using human stem cells and their differentiated derivatives in drug and toxicology screen. Our understanding of most of the basic cellular process underlying both stem cell self-renewal, maintenance and differentiation are still very limited and it will be essential to expand our knowledge in this area if stem cells are also to reach their full potential in this area.

Once again the present paradigm of hematopoietic stem cell production and usage shows us this. There is still, decades after the first hematopoietic stem cell/bone marrow transplant, a requirement for more stem cells for advanced therapies. Our increased understanding of hematopoietic stem cell biology (such as the role of HoxB4 in stem cell expansion) derived from basic research programs, offers new options for deriving populations for cell based therapies. The same basic understanding derived in basic embryonic stem cell research will similarly support clinical developments. As such applying the most advanced systematic techniques to embryonic stem cell studies is an essential adjunct to current research approaches.

Proteomics

Proteomics is a technology platform that aims to characterize proteins in their biological context in a medium to high throughput scenario. This was mainly a technology-based field, driven initially by the development of mass spectrometers with the speed and sensitivity amenable for large scale analysis of peptides, followed by sophisticated miniaturized chromatographic systems. It has more recently, been complemented by an expanding toolbox of bioinformatic applications that have allowed the interpretation of large sets of mass spectrometric data. As a result, proteomics today includes a multitude of techniques such as fractionation strategies for cell organelles and enrichment steps for the selective isolation of specific classes of proteins or peptides (e.g. to identify specific posttranslational modifications critical in regulating cell fate). There are now a wide variety of mass spectrometers available for the confident identification of proteins using either commercial or open source software tools. The strength of this set of techniques is its high modularity and flexibility that can be adapted to the biological question that needs to be addressed. Most importantly, the ability to relatively or absolutely quantify proteins in different cell populations allows proteomics to move to a new level. With a large body of effective technology in place (and more sensitive instruments in the pipeline), the true challenge now is to integrate proteomics into the full spectrum of biological and biomedical research, challenging the creativity of both the biologist and the analytical chemist.

Proteome Biology of Stem Cells

Considering the many challenges in stem cell biology there is a pressing need for the implementation of proteomic applications. This is beginning to be realized by a growing number of scientists who have started to chart the proteome of individual primary stem cells and stem cell lines and their differentiated derivatives, to define a subset of stem cell-specific proteins, or to identify differentiation-specific proteins that can be used as benchmarks for the intermediate or terminal steps of differentiation of cells. Critically these approaches are also providing clues on the signal transduction pathways and transcription factor cascades that drive each differentiation step. Importantly, recent work on stem cells using proteomics has shown that transcriptome analyses do not give a full guide to developmental change in stem cells, and protein interactions (which can only be discovered systematically using proteomic approaches) yield important new concepts on processes regulating development. Stem cell biology and proteomics are both highly specialized scientific domains, however, so they are presently only rarely united in one person or even one lab or institute. The only way to bridge this gap and derive optimal benefit from what each field has to offer, is to bring together the specialists from both fields to discuss needs, possibilities, requirements and conditions that will have to be resolved before collaborative efforts can be successful. The current initiative is a first step in this direction. It envisages providing a platform to discuss the many technical and biological issues to be addressed, either through discussions at existing conferences (HUPO, ISSCR), or at dedicated meetings/discussion groups, possibly linked by video conferencing.

We are of course aware of the International Stem Cell Initiative for benchmarking human embryonic stem cells. There are elements of proteomic techniques which serve the agenda of benchmarking initiatives. This is only one element in the panoply of approaches that mass spectrometry/proteomics offers stem cell biology (e.g. processes of protein acetylation/phosphorylation in developing stem cells, mapping transcription factor interactions in development, absolute quantification of chromatin associated or nuclear proteins; cell surface marker discovery).

Since a targeted initiative in this area of research is likely to be beneficial for many researchers and raise interest in the value of proteomics amongst stem cell researchers we propose to initiate a new HUPO Initiative named “Proteome Biology of Stem Cells”

Goals and deliverables

Long term:

- The initiative seeks to provide a world wide platform for investigators in stem cell proteomics, aiming to effectuate the implementation of proteomic technology in stem cell research to further our understanding of stem cell biology.
- The initiative will bring together leading specialists from both stem cell and proteomics communities, to discuss needs, possibilities, requirements and conditions for setting up collaborative efforts.
- The initiative will serve to promote proteomics in an area of great biologic relevance, and thereby will enhance the leadership of HUPO in this field.

Phase I (year 1):

- The initiative will be the platform to discuss which issues in stem cell biology are most urgent and require proteomic analysis. Conversely, novel analytical strategies will be discussed that would be required to address specific issues in stem cell biology
- The initiative will investigate possibilities for funding of collaborative efforts, both from stem cell and proteomic alliances.
- The initiative will promote collaborations, both bilateral and across many labs. These could relate to similarities and differences between cell lines, culture conditions, self-renewal and differentiation, protein networks and posttranslational modifications. During this phase, sub-projects will be defined and project leaders will be identified.
- The initiative will discuss how cell lines available to few or individual labs can be used or made available for integrative or comparative proteomic studies. This will include practical issues related to sample collection and processing for proteomic analysis. Contact will be sought with the International Stem Cell Initiative to discuss common logistic and organisational issues that may be of mutual benefit.
- The initiative will promote joint dissemination of results acquired in stem cell proteomics studies, possibly via a dedicated issue of high impact stem cell or proteomics journals, the latter supported by HUPO.
- Inaugural sessions for the initiative are proposed for the upcoming meetings of HUPO and ISSCR. At these meetings, an agenda should be set for the short term, which should be further discussed at a dedicated international meeting where stem cell biologists and proteomics experts can discuss the most effective way forward (e.g. definition of sub-projects).

Phase II (year 2 onwards):

- Proteomic datasets generated through the initiative will be analyzed and interpreted compliant with guidelines and standards produced by other HUPO initiatives (PSI). Upon publication, these datasets will be made publicly available through designated databases (e.g. PRIDE).
- The initiative will be a platform for organized efforts for publication of review papers and meeting reports

General and organisational issues:

- Contact with other HUPO initiatives will be sought for advice on setting up bioinformatic resources, dedicated databases and a website to facilitate sharing and exchange of data, and to enhance productivity within the initiative. One of the members will oversee setting up such an infrastructure.
- Endorsement of the HUPO initiative by ISSCR will secure participation of leading investigators from both fields, broad coverage of cell lines and proteomic technologies, and support from both organizations.
- Progress of the initiative will be reported at the annual world meetings of HUPO and ISSCR. The initiative will regularly report on its progress via HUPO supported journals
- The initiative will organize workshops and educational sessions at HUPO and ISSCR meetings

Management

The initial outline of this proposal has been endorsed by leading researchers from both the stem cell and proteomic communities across the continents (see below for names). Representatives from both fields will serve as chairs and co-chairs, guaranteeing adequate interactions. The executive committee will consist of 6 people, ie. two chairs and four co-chairs, representing both communities and all continents.

Chairs and co-chairs will serve for three years, and will meet together with the director of the HUPO at least once a year.

The responsibility of the executive committee is to:

- provide guidance in initiation of and reporting by sub-projects
- organise workshops during HUPO and ISSCR meetings
- report to the HUPO headquarters on a regular basis
- report to the ISSRC headquarters on a regular basis

Although the executive committee still needs to be assembled / elected, we foresee the following candidates

Chair(s)

- Albert J. R. Heck (Europe, Netherlands Proteomics Centre)
- Paul J. Simmons (USA, President ISSCR)

Co-chairs

- Tony Whetton (Europe, University of Manchester)
- Bonghee Lee (Asia, Seoul, Korea)
- Kim Dong-Wook (Asia, director of Korea Stem Cell Research Center)
- Martin Pera (USA, Monash University)

The following individuals have endorsed the current proposal and have expressed their commitment to the initiative, as further indicated in detail in the appendix:

Albert Heck (Utrecht University)
Jeroen Krijgsveld (Utrecht University)
Christine Mummery (Utrecht University and Hubrecht Laboratory)
Jennifer van Eyk (Johns Hopkins, Baltimore)
Bonghee Lee (Seoul, Korea)
Youngmok Park (Seoul, Korea)
Kim Dong-Wook (director of Korea Stem Cell Research Center)
Philip Andrews (U. Michigan, Ann Arbor)
Sue O'Shea (U. Michigan, Ann Arbor)
Tony Whetton, (Manchester, UK)
Matthias Mann (MPI Martinsried)
Mahendra Rao (Invitrogen)
Paul J. Simmons (President ISSCR)
Glyn Stacey (Director for the UK Stem Cell Bank)
Martin Pera (UCLA)
Peter Andrews (Sheffield University, UK)
Ihor Lemischka (Princeton University)
Ron McKay (NIH)
Nancy Witty (Executive Director, ISSCR)

Funding

At the moment funding for this area of research is at good level. For instance in Korea the Ministry of Science and Engineering has provided Dr. Kim Dong-Wook, the director of Korea Stem Cell Research Center, a budget of 138 million U$ for 10 years. Dr. Kim Dong-Wook is very supportive for the Korean research of stem cell proteomics. Also in the US and Europe similar initiatives are under way or already initiated. To organize meetings we will tap-in on existing meetings such as the HUPO and ISSCR organized meetings, which may help us to reduce costs and moreover help us to disseminate the results of this initiative to a broader audience.