What has been achieved?

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This note has description of what I believe are good achievements. As good, I mean results which may be of use in practical clinical work.

This can be in clinic already now:

1. Functional Molecular Diagnostic (FMDx)
FMDx is a set of assays performed on living and processed tumor cells obtained from a patient upon surgery or as a biopsy. These assays measure in a real time how the patients' tumor may respond to different drugs before the patient is offered treatment, and whether the tumor is of an aggressive type. The successfulness of FMDx is based on novel proprietary technologies. FMDx is described in details in the FMDx section of this homepage.
FMDx has been used to help many patients, and with good response from clinicians. The most frequently requested is the test with circulating tumor cells, followed by organ culture, proteomics and biochemical tests.
FMDx tests are also a great source of information about fundamental mechanisms of carcinogenesis.

2. Markers for early detection of breast cancer
Early stages of breast cancer may not manifest any symptoms, and therefore are difficult to detect. Early detection may increase survival up to 95%, including a long term 10-years survival.
Three proteins (cSHMT, Tbx3 and utrophin) were found to correlate with early stages of breast cancer. Research stage of this work is completed, and all is ready for development and production of a diagnostic kit. The idea is that women may take this very simple and non-expensive test at places of the primary health care, as a part of yearly medical examination. The test requires an analysis of one drop of blood.

3. Proteome signatures for prediction of aggressiveness of human breast cancer
Proteome signatures of proliferative progression and invasiveness have been obtained. These signatures are based on our proteome profiling of various steps of carcinogenic transformation, and on profiling of clinical samples. Application of these signatures to clinical samples allows prediction whether tumor will be aggressive and metastatic, or it will be indolent.

4. Implementation of meta-data analysis for individualization of treatment of cancer patients
We developed an approach to significantly improve individual assessment human breast cancers, and to personalize treatment of patients. This approach is based on a full-scale analysis of each tumor individually, and further meta-data analysis.
In other words, our approach allows detection of individual features of each tumor. This allows identification of drugs that would be helpful for that given patient.

To attention of drug developers

5. Assays for monitoring efficiency of TGFbeta signalling-addressing drugs in in vivo models
We developed a know-how for monitoring in the human blood the efficacy of drugs acting on TGFbeta signalling. This may be of importance for monitoring of PK/PD of drugs in the blood.

7. Proteomics-based technology for monitoring of the specificity of kinase inhibitors
This is a technology developed to monitor specificity of kinase inhibitors in an unbiased way, when any kinase in a cell which can be affected by a tested compound, will be detected and then identified. In one run, it is possible to see which kinases are inhibited by a compound by probing the whole cellular kinome.

Important findings which have been made so far and are reported in publications:

Implementation of meta-data analysis as a tool to assess individual features of tumors, and to develop a personalized treatment for a given patient.
** Attarha S., Mints M., Andersson S., Souchelnytskyi S. Individualized proteome profiling of human endometrial tumours improves detection of new prognostic markers. (2013) Br. J. Cancer, doi: 10.1038/bjc2013.359.
**Zakharchenko O., Greenwood C., Lewandowska A., Hellman U., Alldridge L., Souchelnytskyi S. Meta-data analysis as a strategy to evaluate individual and common features of proteome changes in breast cancer. (2011) Cancer Genomics and Proteomics, 8, 1-14.

New mechanism in TGFbeta signaling, relevant to breast cancer. We showed that TGFbeta can regulate protein synthesis by direct phosphorylation of eEF1A1 by TGFbeta type I receptor.
This work published in Current Biology was a featured article, and of top 10 downloads, according to the Cell Press.
Lin K.W., Yakymovych I., Jia M., Yakymovych M., Souchelnytskyi S. Phosphorylation of eukaryotic elongation factor eEF1A1 at Ser300 by type I transforming growth factor-beta receptor results in inhibition of mRNA translation. (2010) Current Biology, 20(18), 1615-1625.

Proteome signature of immortalization of human breast epithelial cells.
This signature can be used for diagnostics of malignant and benign neoplasia.
Jia M., Souchelnytskyi N., Hellman U., O Hare M. Jat P.S., Souchelnytskyi S. Proteome profiling of immortalization-to-senescence transition of human breast epithelial cells identified MAP2K3 as a senescence-promoting protein which is down-regulated in human breast cancer. (2010) Proteomics Clinical Applications, 4, doi: 10.1002/prca.201000006.

Proteome signature of acquiring of the high proliferation rate in human breast cancer.
Bhaskaran* N., Lin* K.W., Gautier* A., Woksepp H., Hellman U., Souchelnytskyi S. Comparative proteome profiling of MCF10A and 184A1 human breast epithelial cells emphasized involvement of CDK4 and Cyclin D3 in cell proliferation. (2009) Proteomics Clinical Applications, 3(1), 68-77. *Equal contributions.

Systemic analysis of TGFbeta signalling; pro-zone effect in regulation of Ras/Raf/Erk signalling.
Bhaskaran N., Souchelnytskyi S. Systemic analysis of TGFbeta proteomics revealed involvement of Plag1/CNK1/ RASSF1A/Src network in TGFbeta1-dependent activation of Erk1/2 and cell proliferation. (2008) Proteomics, 8 (21), 4507-4520.

First report of O-glycosylation profiling of TGFbeta signalling.
Iwahana H., Yakymovych I., Dubrovska A., Hellman U., Souchelnytskyi S. Glycoproteome profiling of TGFbeta signalling: non-glycosylated CIDE-A inhibits TGFbeta1-dependent apoptosis. (2006) Proteomics, 6, 6168-6180.

First phosphoproteomics study of TGFbeta signalling.
Stasyk* T., Dubrovska* A., Lomnytska M., Wernstedt C., Heldin C.-H., Hellman U., Souchelnytskyi S. Phosphoproteome profiling of transforming growth factor-beta signalling: abrogation of TGFbeta1-dependent phosphorylation of TFII-I enhances cooperation of TFII-I and Smad3 in transcription. (2005) Mol. Biol. Cell, 16, 4765-4780. *Equal contribution

New concept for intracellular signalling: first report of a direct interaction between a Ser/Thr kinase receptor (BMPRII) and a Tyr kinase receptor.
Hassel S., Yakymovych M., Hellman U., Rönnstrand L., Knaus P., Souchelnytskyi S. Interaction and functional cooperation between the serine/threonine kinase bone morphogenetic protein type II receptor with the tyrosine kinase stem cell factor receptor. (2005) J. Cellular Physiology, DOI 10.1002/jcp.20480, in paper: (2006) 206, 457-467.

Description of 3 markers for early detection of breast and ovarian cancer.
Lomnytska M., Dubrovska A., Hellman U., Volodko N., Souchelnytskyi S. Increased expression of cSHMT, Tbx3 and utrophin in plasma of ovarian and breast cancer patients. (2005) Int. J. Cancer, doi10.1002/ijc.21332, in paper: (2006) 118, 412-421.
*Patent, Protein markers for the diagnosis and prognosis of ovarian and breast cancer. US 11/829,360, July, 27, 2007.

Definition of rules for the application of systems biology to proteomics.
Souchelnytskyi S. Bridging proteomics and systems biology: what are the roads to be travelled? (2005) ? Proteomics, 5, 4123-4137.

Novel method to study phosphoproteome, on the level of full-length proteins.
Dubrovska A., Souchelnytskyi S. Efficient enrichment for phosphorylated proteins by immobilized metal-affinity chromatography. (2005) Proteomics, 5, 4678-4683.

Two papers which reported a cross-talk between BRCA1 and BRCA2 with TGFbeta/Smad3 signalling, with an impact on breast cancer tumorigenesis.
Dubrovska A., Kanamoto T., Lomnytska M., Heldin C.-H., Volodko N., Souchelnytskyi S. TGFbeta/Smad3 counteracts BRCA1-dependent repair of DNA damage. (2005) Oncogene, 21, 2289-2297.
Preobrazhenska O., Yakmovych M., Kanamoto T., Yakymovych I., Stoika R.S., Heldin C.-H., Souchelnytskyi S. BRCA2 and Smad3 synergize in regulation of gene transcription. (2002) Oncogene, 21(36), 5660-5664.

Description of two types of TbRI kinase inhibitors, including substrate-mimetic.
Yakymovych I., Engström U., Grimsby S., Heldin C-H., Souchelnytskyi S. Inhibition of TGFbeta signaling by low molecular weight compounds interfering with ATP- or substrate-binding sites of the TGF-beta type I receptor kinase. (2002) Biochemistry, 41, 11000-11007, 10.1021/bi025936u.

First proteomics study of TGFbeta signalling, and of TGFbeta role in DNA damage repair.
Kanamoto T., Hellman U., Heldin C.-H., Souchelnytskyi S. Functional proteomics of transforming growth factor-beta1 stimulated Mv1Lu cells; Rad51 as a target of TGFbeta 1-dependent regulation of DNA repair. (2002) EMBO J., 21(5), 1219-1230.

Novel mechanism of the cross-talk in TGFbeta signalling, with an impact on carcinogenesis.
Yakymovych I., ten Dijke P., Heldin C.-H., Souchelnytskyi S. Regulation of Smad signaling by protein kinase C. (2001) The FASEB Journal, 10.1096/fj.00-0474fje, 15 (3), 553-555.

First report of transcriptional activity of Smad7.
Pulaski L., Landström M., Heldin C.-H., Souchelnytskyi S. Phosphorylation of Smad7 at Ser249 does not interfere with its inhibitory role in TGFbeta-dependent signaling, but affects Smad7-dependent transcriptional activation. (2001) J. Biol. Chem., 276 (17), 14344-14349.

First report of phospho-Ser binding domain in Smad4, as a novel concept in intracellular signalling.
Souchelnytskyi S., Tamaki K., Engström U., Wernstedt Ch., ten Dijke P., and Heldin C.-H. Phosphorylation of Ser465 and Ser467 in the C terminus of Smad2 mediates interaction with Smad4 and is required for transforming growth factor -beta signaling. (1997) J. Biol. Chem., 272(44), 28107-28115.

Description of the mechanism of activation and regulation of TGFbeta receptors.
Souchelnytskyi S., ten Dijke P., Miyazono, K., Heldin, C.-H. Phosphorylation of Ser165 in TGF-beta type I receptor modulates TGF-beta1-induced cellular responses. (1996) EMBO J., 15(22), 6231-6240.

Novel mechanism of activation of latent TGFbeta, by protein-protein interaction.
Souchelnitskiy S., Chambaz E.M., Feige J.-J. Trombospondins selectively activate one of the two latent forms of TGFbeta present in adrenocortical cell conditioned medium. Endocrinology, 136(11), 5118-5126.

Novel mode of action of TGFbeta receptors: cooperativity phenomenon.
Sushelnitsky S.I., Stoika R.S. Determination of kinetic parameters of specific binding of the transforming growth factor-beta by normal rat kidney cells of NRK-49F line. (1991) Biol. Membrane, 8(6), 628-632.

Purification of TGFbeta1 on a large scale, first in Europe.
Sushelnitskii S.I., Stoika R.S., Garasko S.I., Shafranskaya G.I., Kusen S.I. The influence of the transforming growth factor-beta and its combination with the epidermal growth factor and insulin on substrate-independent proliferation of cells from normal and tumor tissues. (1989) Cytology, 31(7), 767-774.