Cytomics in predictive medicine

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ABSTRACT

Predictive Medicine aims at the detection of changes in patient's disease state prior to the manifestation of deterioration or improvement of the current status. Patient-specific, disease-course predictions with >95% or >99% accuracy during therapy would be highly valuable for everyday medicine. If these predictors were available, disease aggravation or progression, frequently accompanied by irreversible tissue damage or therapeutic side effects, could then potentially be avoided by early preventive therapy. The molecular analysis of heterogeneous cellular systems (**Cytomics**) by cytometry in conjunction with pattern-oriented bioinformatic analysis of the multiparametric cytometric and other data provides a promising approach to individualized or personalized medical treatment or disease management. Predictive medicine is best implemented by cell oriented measurements e.g. by flow or image cytometry. Cell oriented gene or protein arrays as well as bead arrays for the capture of solute molecules form serum, plasma, urine or liquor are equally of high value. Clinical applications of predictive medicine by Cytomics will include multi organ failure in sepsis or non infectious posttraumatic shock in intensive care, or the pretherapeutic identification of high risk patients in cancer cytostatic therapy. Early individualized therapy may provide better survival chances for individual patient at concomitant cost containment. Predictive medicine guided early reduction or stop of therapy may lower or abrogate potential therapeutic side effects. Further important aspects of predictive medicine concern the preoperative identification of patients with a tendency for postoperative complications or coronary artery disease patients with an increased tendency for restenosis. As a consequence, better patient care and new forms of inductive scientific hypothesis development based on the interpretation of predictive data patterns are at reach.

Keywords: individualized medicine, cytometry, cytomics technology, pediatric cardiology, coronary artery

1. INTRODUCTION

Predictive Medicine aims at the detection of changes in patient's disease state prior to the manifestation of deterioration or improvement of the current status. Such instances may concern multi organ failure in sepsis or non infectious posttraumatic shock in intensive care (1; 2), or the pretherapeutic identification of high risk patients in cancer cytostatic treatment (3, 4) or surgical therapy (5, 6, 7). Early antiinfectious or antishock therapy as well as curative chemotherapy in combination with stem cell transplantation may provide better survival chances for individual patient at concomitant cost containment. Predictive medicine guided early reduction or stop of therapy may lower or abrogate potential therapeutic side effects. Further important aspects of predictive medicine concern the recognition of preasthmatic and early rheumatic disease patients as well as the preoperative identification of patients

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with a tendency for postoperative complications (8) or coronary artery disease patients with an increased tendency for restenosis (6, 9, 10).

Once initiated, one realizes that everydays medicine is full of predictive issues. They are present in a variety of severe diseases like cancer, leukemias, rheumatoid diseases, diabetes and asthma but also when considering infections in newborns, pediatric patients (11; 12), adults or elderly patients as well as bleeding risks during surgery a.o. Individualized disease course predictions for currently envisaged standard therapies would definitively allow in many instances early curative interaction by specific therapeutic measures prior to the occurrence of irreversible tissue destruction with its inherent potential to incapacitate the patient in many instances on a longer run.

Challenge: The obvious challenge is to define a generalizable access to individualized predictions (13). Cell oriented analysis is essential in this effort because diseases are characterized by significant deviations from usual molecular processes in cellular systems or organs. The determination of the molecular phenotype of discrete cell populations by single cell oriented analysis is therefore particularly promising and represents evidence based medicine at the cellular level (EBM). Molecular cell phenotypes represent the result of patient's genotype and exposure to disease inducing causes. While the genotype seems most important at first glance, the medical reality indicates that exposure to disease inducing causes is frequently more important for disease generation than the genetic background. This is exemplified by individuals who are genetically highly susceptible to allergy or rheumatoid arthritis but are unlikely to develop disease without exposure while heavy exposure may provoke disease in genetically relatively resistant individuals.

cytomics: multimolecular cytometric analysis of the cellular heterogeneity of cytomes (cellular systems or organs), cell system analysis

Cytomics, as the multimolecular cytometric analysis of the cellular heterogeneity of cytomes (cellular systems/organs/body) access a maximum of information on the apparent molecular cell phenotype in disease. The term cytomics carries a disciplinary aspect. It was coined by molecular botanists (14) in analogy to genomics and proteomics, describing the analyses of the genome, the proteome and the "cytome" (http://www.genomicglossaries.com/content/omes.asp). In contrast to the earlier term system cytometry (15), it is method independent. The European Working Group on Clinical Cell Analysis (EWGCCA, http://www.ewgcca.org) and the Clinical Cytometry Society (CCS, http//cytometry.org) promote medical and clinical cytomics while the International Society of Analytical Cytology (ISAC, http://www.isac-net.org) sets presently a focus on the basic research oriented cell biological, molecular biology, bio- and nanotechnology aspects of cytomics.

Medical Bioinformatics: The cell oriented determination of molecular parameters by cytometry, multiplex bead assays or cell population and single cell oriented microarray technologies generates high amounts of data. A major challenge consists in their predictive medicine oriented analysis. The available information is usually extracted in a fragmentary way by computer assisted identification and characterization of a few cell populations or gene clusters of interest. Alternatively the entire available information can be screened exhaustively by multiparametric clustering (16, 17), data mining or other procedures for diagnostic purposes using hypothesis driven analysis strategies (18). They frequently require mathematical, statistical or other assumptions which may unintentionally bias the results. Assumption free algorithmic evaluation concepts like data sieving (13, http://www.biochem.mpg.de/valet/classif1.html) as a bottom-up approach seem of particular interest for the detection of unknown molecular disease mechanism which are inaccessible to a-priori top-down oriented hypothesis. Following identification of the predictively important data patters, a major task will consist in the consensus driven development of standardized predictive disease classifiers for clinical purposes.

Patient Groups: The ultimately desired high statistical significance of results for clinical applications is initially in conflict with the collection of high amounts of multiparametric information in the search for predictive parameters. A two phasic strategy is therefore appropriate. During the *pilot phase*, the utmost number of multiparametric information is collected in clinically well characterized patient groups at an acceptable minimum of statistical stringency e.g. a significance level of $p<0.05$ or $p<0.10$. The majority of uninformative parameters will be eliminated at this stage during data sieving or multivariate analysis (12; 6). In the *second phase*, the reduced numbers of informative parameters for disease course prediction are analyzed in statistically large patient groups (3, 4). This will provide exact numbers for the reliability of individualized disease course predictions and eliminate pseudo-informative parameters which have slipped for random statistical reasons into the group of informative parameter during the first phase. Informative parameters may likewise have been lost for random statistical reasons into the group of non-informative parameters during the initial phase. They may, however, be recoverable during the deductive hypothesis and concept forming phase from the molecular context of the predictive parameter pattern determined during the first phase.

Prognosis and Prediction: The prognostic information of clinical and molecular parameters in large patient groups is typically utilized for risk and therapy stratification. The well recognized problem remains, however, that therapy responders and non-responders cannot be identified prior to therapy. The potential for the pretherapeutic identification of high risk non-responder patients by predictive medicine is therefore of high clinical interest because it helps to provide early therapeutic alternatives for high-risk patients by objective criteria.

Personalized Medicine: Unlike prenatal screening for rare genetic diseases which is restricted to a particularly important phase in human development, the cytomics oriented approach to predictive medicine provides an entry into personalized or individualized medicine in a very general sense. Based on disease course predictions at a >95% or > 99% accuracy level, current standard therapies can be modified by the clinician on objective grounds according to the specific requirement of the individual patient. Clinical benefits will concern a better direction of diagnostic and therapeutic efforts to patients in need as well as a potential decrease of unwanted side effects by an earlier stop of therapy. Patients who will not respond to an envisaged therapy can be shifted immediately to alternative treatment schedules thus lowering the risk of side effects and costs.

Analytical techniques: Predictive medicine is best implemented by cell oriented measurements e.g. by flow or image cytometry. Cell oriented gene or protein arrays as well as bead arrays for the capture of solute molecules form serum, plasma, urine or liquor are equally of high value. The increasing miniaturization of cytometers through semiconductor light sources and laboratory chip technology makes predictive medicine of interest for general clinical and ambulant medicine as point of care technology. Like earlier driving forces in the continuously expanding cytometry field, predictive medicine represents a new challenge for clinicians, molecular biology and bioinformatics oriented cellular scientists in collaboration with industrial instrument and assay development (19 - 23). The contributions in this supplement represent an initial effort into this new direction of cytometry.

2. METHODOLOGY

2.1 Cytomics Technologies

Cytometric analysis is an ideal technological platform for the novel clinical concept of predictive medicine. Predictive medicine aims at the detection of changes in patient's disease state prior to the manifestation of deterioration or improvement. Typical examples concern multi organ failure in sepsis or non infectious posttraumatic shock in intensive care, or the pre-therapeutic identification of high risk patients in surgical therapy (overview in 24). Individualized disease course predictions for currently envisaged standard therapies would definitively allow in many instances early curative interaction by specific therapeutic measures prior to the occurrence of irreversible tissue destruction with its inherent potential to incapacitate the patient in many instances on a longer run. Predictive medicine is based on the analysis of the CYTOME of an individual patient. Cytome/**Cytomics**, is the multimolecular cytometric analysis of the cellular heterogeneity of cytomes (cellular systems/organs/body) access a maximum of information on the apparent molecular cell phenotype in disease. The term Cytomics carries a disciplinary aspect. It

was coined by molecular botanists in analogy to Genomics and Proteomics, describing the analyses of the genome, the Proteome and the Cytome (http://www.genomicglossaries.com/content/omes.asp). Although the term is method independent Cytometry technologies provide typical CYTOMICS platforms (13).

2.2. Structuring of Predictive Medicine by Cytomics Studies

In order to yield the analytical tools for predictive medicine by Cytomics a generalized experimental protocol was developed that is suitable for various clinical settings. This concept comprises of three subsequent basic steps that allow to cost effectively and rapidly come to concluding algorithms and assays.

Step 1
Aim of Step 1 is to detect parameters of high predictive value that could be useful to predict the patients "fate". In this 1st step samples from a limited group of patients (20-50) with or without problematic outcome are analyzed using a broad variety of parameters and instruments (see 2.2). The selection of the parameters is hypothesis driven. However, it is not confined to those strictly definable by a hypothesis but should be set as broad as possible. The concept behind this Cytomics approach is, to test as many parameters as possible in order to avoid loss of possibly highly valuable parameters that would not be selected by theory alone. This high amount of data is now reduced to those giving a predictive pattern of high sensitivity, specificity as well as positive and negative predictive value using "datamining" or "**datasieving**" procedures. Here, all these discriminating parameters should ideally be above 90 %.

Step 2
Aim of the 2nd step is to optimize the predictive data pattern and the algorithms. To this end, a small group of prospectively analyzed patient samples is used. Now the algorithms from step 1 are applied for this "unknown" patient group and should result in a similarly good discrimination.

Step 3
In step 3, the data patterns defined and optimized in the previous steps are applied for a prospective, and ideally randomized, large patient group. Whereas here the number of analyzed patients should be as large as possible (> 200) the number of parameters analyzed is now reduced to those defined earlier. If the determined predictive algorithms are suitable with an acceptable predictive values of > 90% in the final step this predictive system may be implemented into the daily clinical decision making.

Step 4
In step 4, finally, the parameters of high predictive value that were picked by the data sieving algorithms and proved to be predictive in the prospective clinical setting may be used for the development of novel treatment strategies.

2.3 Data Analysis

For Predictive medicine various algorithms are applicable for data analysis, i.e. distinction between groups of patients who differ in outcome. We have used among others discriminant analysis or CLASSIF 1 (8). Both approaches yield basically identical results. Other software approaches for discrimination include neural network, logistic regression or fuzzy logic approaches (18). Most of these analyses can be performed by commercially available software.

3. RESULTS/EXAMPLES

In the following typical examples of ongoing studies from our group are presented that exemplify the procedures for predictive medicine. In these studies we have finished Step 1 or 2 and are about to start step 3 of the studies.

3.1 Prediction of Protein losing eneteropathy in children with univentricular heart

Protein-losing enteropathy (PLE) is a late complication of the Fontan type surgery for univentricular heart characterized by massive enteric protein loss. The pathogenesis of PLE is not fully understood and it is unclear why the onset of PLE varies widely and occurs months or even years after surgery. Besides characteristic laboratory findings a typical cellular feature concerns the almost selective loss of $CD4^+$ lymphocytes at an only slightly changed $CD8^+$ lymphocyte count. The present pilot study aimed to test whether immunological or laboratory parameters differ in patients at risk for PLE.

For this study (12) from children (n=15) with Fontan type circulation extensive cellular, humoral and clinical laboratory data were analyzed. Patients without enteric protein loss (group I, n=8), with transient phases of enteric protein loss in the absence of gastric infections (group II, n=6), and one PLE patient (group III) were distinguished. The 90 data columns obtained in phases with normal serum protein levels were compared.

Clear differences were apparent between patients prior to PLE onset (group III), patients that in at least one occasion exhibited PLE signs (group II) and patients without detectable PLE signs (Group I). The most discriminatory parameters between the three patient groups were NK (natural killer) cell and $CD8^+TCR\alpha\beta^+$, $CD8^+TCR\gamma\delta^+$ cell counts including sL-selectin, IgE and Ca^{2+} (Average recognition index: 91.5%, negative/positive prediction/sensitivity/specificity > 83%).

This study exemplifies that the Cytomics approach provides the possibility to predict outcome from many different sources of data obtained. As demonstrated in Table 1 clinical data (Tab. 1c) or serological data (Tab. 1b) or cellular immunological i.e. flow cytometric data (Tab. 1.a) all capable to discriminate between samples from the three groups of patients. The data patterns were calculated from more than 90 data columns and lead to their reduction down to four to seven parameters that sufficiently discriminate risk from non risk patients. Note, however, that the composite data pattern that has been calculated from all data obtained (Tab. 1.d) has the best results regarding discrimination.

This is one example that demonstrates an application in a very rare complication of a fairly seldomly occurring congenital disease. In this setting it takes a long time to acquire data of a statistically relevant number of patients. Therefore, the Cytomics approach is preferable, wherewith as many parameters as possible and sensible are acquired per patient sample. This approach helps in that in the final analysis in the end, or in interim data viewing during the study, the risk of loosing important data can not be outruled but is smaller compared to other type of studies.

The Predictive Medicine approach allows then to select parameters that may be useful in future not only to have a tool for risk assessment at hand but also to develop new ideas about the development of the disease. In the given example the data indicate that autoimmunity may be involved in this disease. A hypothesis, that is now further tested in new clinical studies. The results of this study seem to provide access to the early detection of PLE patients.

a. Flow cytometry panel

Selected parameters			Confusion matrix		
NK cell count			Predicted group		
B cell count	Clinical		I	II	IIII
$CD8^+TCR\alpha\beta^+$ cell count	status	n	%	%	%
$CD3^+$ CD45RO/RA MFI ratio	Group I	63	**85.7**	14.3	0.0
$CD3^+8^+$ cell count	Group II	26	23.1	**76.9**	0.0
$CD8^+TCR\gamma\delta^+$ cell count	Group III	5	20.0	0.0	**80.0**
	Prediction		Neg	Pos	Pos
F-probability = 0.10			90.0 %	69.0 %	100.0 %
	ARI = 84.5%			72.7 %	
				Pos Pred Group II + III	

b. Serological panel

Selected parameters			Confusion matrix		
sIL-2r			Predicted group		
sE-Selectin	Clinical		I	II	IIII
sL-Selectin	status	n	%	%	%
sHistamine	Group I	63	**82.5**	14.3	3.2
C5a/C5 ratio	Group II	23	26.1	**60.9**	13.0
IgE	Group III	5	0.0	20.0	**80.0**
	Prediction		Neg	Pos	Pos
F-probability = 0.10			89.7 %	58.3 %	50.0 %
	ARI = 76.9%			67.6 %	
				Pos Pred Group II + III	

c. Clinical laboratory panel

Selected parameters			Confusion matrix		
Ca^{2+}			Predicted group		
WBC count	Clinical		I	II	IIII
Monocytes %	status	n	%	%	%
Hemoglobin	Group I	63	**84.1**	6.3	9.5
	Group II	21	28.6	**71.4**	0.0
F-probability = 0.10	Group III	5	0.0	0.0	**100.0**
	Prediction		Neg	Pos	Pos
			89.8 %	79.0 %	54.5 %
	ARI = 82.0%			66.7 %	
				Pos Pred Group II + III	

d. All parameters

Selected parameters			Confusion matrix		
NK cell count			Predicted group		
$CD8^+TCR\alpha\beta^+$ cell count	Clinical		I	II	IIII
$CD3^+8^+$ cell count	status	n	%	%	%
$CD8^+TCR\gamma\delta^+$ cell count	Group I	63	**93.7**	6.3	0.0
sL-Selectin	Group II	24	16.7	**83.3**	0.0
IgE	Group III	5	0.0	0.0	**100.0**
Ca^{2+}	Prediction		Neg	Pos	Pos
			93.7%	83.3%	100.0%
F-probability = 0.02	**ARI = 91.5%**			86.2%	
				Pos Pred Group II + III	

Table 1: Examples for predictive patterns applicable to discriminate children at risk for protein losing enteropathy)Chapter 3.1.). Data are excerpted from (12)

3.2 Prediction of in-stent restenosis by pre interventional activation grade of circulating neutrophils

Restenosis of coronary artery stents used for interventional opening of coronary artery oclusion is a serious problem in cardiology and may lead to severe clinical problems. The activation status of the inflammatory system has been suggested to play an important role in predicting restenosis. Activation of leukocyte adhesion molecules occur after coronary intervention and the level of activation correlates to restenosis. However, little is known about the specific role of adhesion molecules before intervention. The purpose of this study concerned the search for differences in the expression level of selected adhesion molecules to identify suitable tools for the pre-procedural identification of restenosis patients prior to angioplasty.

In this study (6) blood samples of 31 patients undergoing elective coronary angiography were obtained just before intervention. Seven healthy volunteers were also enrolled. Surface expression of leukocyte adhesion molecules Mac-1 (CD11b/CD18), LFA-1 (CD11a/CD18), L-Selectin (CD62L), ICAM-1 (CD54) and MHC-II (HLA-DR) were assessed by flow cytometry. Patients with a successful angioplasty received a follow-up angiography after six months.

According to the clinical and angiographic data, patients were divided into four groups: control (n=7), no restenosis (n=11), restenosis (n=4) and advanced coronary artery disease (CAD, n=9). The restenosis group and the advanced CAD group showed higher expression of Mac-1 and LFA-1 on monocytes and neutrophils compared to the other groups. Using the pre-procedural expression levels patients with restenosis could be predicted by discriminant analysis with CD11a, CD11b and CD18 (average recognition index = 95.5%).

The data of this pilot study indicate that pre-procedural activation status of CD11a and CD11b may play a role in the subsequent development of restenosis. Moreover, CD11a, CD11b and CD18 may be helpful as indicators for the progression of CAD.

3.3. Prediction of acute post-operative escalating inflammatory response following cardiovascular surgery in children by pre-operatively acquired flow cytometric data

The development of post-operative edema and effusion (POEE) following cardiopulmonary bypass (CPB) surgery in children retards recovery and may aggravate into post-pericardiotomy (PPS), capillary leak syndrome (CLS) or multi-organ failure (MOF). PPOE affected children show different pre-operative serum levels of circulating cytokine and adhesion molecules as complication free children. These differences can be used for preoperative risk assessment but their determination is time consuming, costly and a substantial blood volume is required. Under the concept that altered serum levels of the above molecules may also be reflected in altered antigen expression on circulating blood leukocytes, the predictive potential of flow cytometric (FCM) leukocyte immunophenotyping as a sensitive, fast and little blood requiring methodology was explored.

In this study (8) 24h pre-operative blood samples from 49 patients (3 to 18 yr.) were stained with monoclonal antibodies for adhesion molecules (ICAM-1, LFA-1, Mac-1) or constitutive/activation markers (CD4, CD14, CD16, CD25, CD54, CD69, HLA-DR) and measured on a microbead calibrated FCM. Neutrophils, monocytes and eosinophils of POEE patients express higher preoperative levels of LFA-1 and monocytes higher levels of HLA-DR as well as other activation markers (all $p<0.03$). Over 89% of the patients were correctly classified by two different discriminant analysis methods (sensitivity: >76%; specificity: >86%; positive prediction: >80%; negative prediction: >83%).

Granulocytes and monocytes of postoperative POEE patients exhibit significant preoperative immune activation, suggesting increased risk for patients with atopic/allergic predisposition. Surgical trauma and CPB cause additional immune activation leading to POEE by a summative response. Most POEE risk patients can be preoperatively identified by the use of data pattern analysis on FCM derived parameters.

3.4 Prediction of acute post-operative escalating inflammatory response following cardiovascular surgery in children by serological and routine laboratory data

Post-operative effusions and edema (POEE) and capillary leak syndrome (CLS) in children after cardiac surgery with cardiopulmonary bypass (CPB) constitute considerable clinical problems. Overshooting immune response is held responsible as the cause. We investigated in a prospective study whether preoperative immune status differences exist in patients at risk for post-surgical effusions and edema and to which extent these differences permit preoperative outcome predictions.

For this study (25), one day preoperative serum levels of immunoglobulins, complement, cyto- and chemokines, soluble adhesion molecules and receptors as well as clinical chemistry parameters like differential counts, creatinine, blood coagulation status (altogether 56 parameters) were analyzed in peripheral blood samples of 75 children (3-18yr) undergoing CPB surgery (29 with POEE within the first post-operative week).

Preoperative elevation of the serum level of C3 and C5 complement components, TNF-α, percentage leukocytes that are neutrophils, body weight and decreased percentage of lymphocytes (all $p<0.03$) occurred in children developing POEE. While single parameters did not permit individual predictions, >86% of the POEE patients were correctly predicted by two different multivariate discriminant statistics and algorithmic data mining classifiers each selecting nine partially overlapping parameters. The prediction quality was independent of the congenital heart defect.

Indicators of inflammation were selected as risk indicators by explorative data analysis. This suggests that preoperative differences in the immune system and capillary permeability status exist in patients at risk for post-operative effusions. These differences are suitable for preoperative risk assessment and may be applied for the benefit of the patient and cost effectiveness.

4. DISCUSSION

The broad range of clinical applicability of Predictive Medicine by Cytomics was recently presented in a focus issue of Cytometry. Basically, all clinical settings that demand the knowledge of the future of a patient, i.e. the development of his or her disease is an object of predictive medicine. The fields of application range from acute responses such as sepsis, SIRS or organ dysfunction syndrome to problem that will arise a long time after the test. To the latter the following clinical examples belong: Development of malignancies, transplant rejection, autoimmunity, among others. Once one starts to look at disease development one will find many patterns that are of possible predictive value and one can suspect that nearly all fields of clinical application may once in future be supported by Predictive Medicine. The benefit for the patient, his or her relatives and for the budget of the hospital are clear-cut.

This concept requires some changes in the thinking of disease and of the role of the physician in the process of its management. One very interesting example is the preoperative prediction of an outcome in between complicated and extremely stressful clinical procedures are performed: Cardiac surgery, extracorporeal circulation, medication etc.. In our pilot studies several years ago, the view of a surgeon was that as long he is doing an excellent job the outcome will be excellent as well. It is clear that an excellent surgical care is on pivotal aspect for the patients recovery. However, results of the recent years show that this is not unequivocally the case.

The conclusion is, that there are individual variations, i.e. a predisposition, towards the response to surgical trauma and related circumstances of a surgery. Our findings but also actual results demonstrate that the response to surgical trauma is also influenced by genetical factors and environmentally influenced (8, 26).

A prominent example is the predisposition of an individual to respond to lipopolysaccharide (LPS), a component of the surface of Gram-negative bacteria that induces sepsis and septic shock. Hypo and hypersensitivity to LPS are dependent on the expression of Toll-like Receptor (TLR) 4. TLR 4 is presented on the surface of circulating monocytes and macrophages of the peripheral blood and binds LPS. This binding then starts an intracellular signaling

cascade and finally induces release of inflammatory cytokines. LPS is released during cardiocirculary arrest during surgery from the gut. Therefore, cardiovascular surgery leads to sepsis-like immune response (27). Mutation of TLR4 leads to hyposensitivity towards LPS (28, 29). Increased expression of functionally active is, in contrast, directly correlated with the response to LPS (29, 30). The response via TLR 4 is further modulated by latent infections, stress, among others (29, 30). Transmission of sepsis response via TLR 4 is only one of several independent pathways (31, 30). Other factors such as sensitivity towards medication, response to foreign surface among others further modulate the immune response leading to difficulty of predicting responses by the investigation of one parameter a such as TLR4 expression or mutation alone.

Considering the vision of the seventies where cytometrists tried to automatically identify cancer cells by flow and image cytometry, the new challenge of a Human Cytome Project extends much further into the standardized molecular description of assembled cellular systems in their full complexity under normal and disease conditions

The fact, that the genome sequence as well as the structural and functional knowledge on all coded biomolecules does not allow by itself to assemble living cells, emphasizes the urgent need for a more systematic molecular analysis of assembled cellular systems by cell oriented approaches. These include flow and image cytometry, advanced microscopy, the various kinds of cell oriented molecular array technologies but also sophisticated bioinformatics to build up standardized relational structures and to generate something like a periodic system of cells and cell systems.

Cytomics, as cell and cell systems research will have a central role in this effort. One obvious clinical benefit will be in future its direct involvement in prediction and individualized medicine.

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