DrugLogics

About the project

The biological sciences are producing massive amounts of information about how cells function in normal or diseased states. There is now so much knowledge that it is becoming possible to use computers in Systems Biology approaches to model the behaviour of cells and reliably predict how they will respond to changes in the environment, or to drugs. Many scientists believe that this new field of *Systems Medicine* will soon make it possible to use computer model simulations to help select the best treatment for individual patients, and allow *personalised medicine*. This requires scientists from many different backgrounds to work together, in order to develop the different technologies and approaches that need to be integrated in order to efficiently use everything we know about specific cells, design a model that mimics the cell's behaviour in a computer program, and produce tools that can be used by doctors in a hospital to offer tailor-made therapy to a patient.

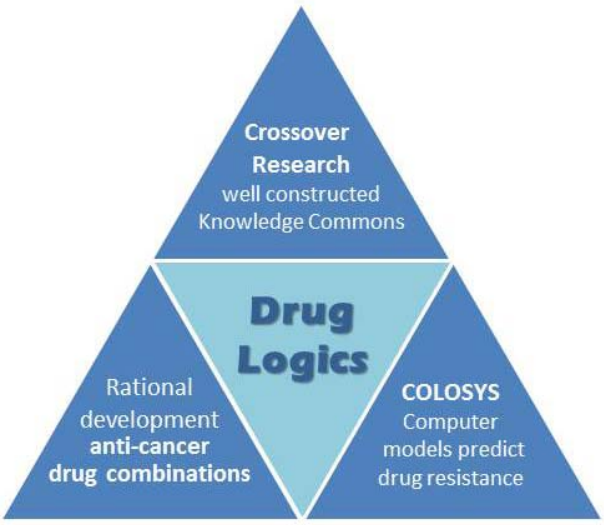

Figure 1: Elements of the DrugLogics project

In the DrugLogics project we will use recent discoveries made in our research at NTNU, integrate different technologies and analyse them as a practical test for treatment of patients with very specific types of cancer.

Key to our research is the development of a broadly enabling **Knowledge Commons** – KC - (Fig 2, left circle) as an overarching resource of well-structured background knowledge that provides essential input for **Systems Biology** (Fig 2, right circle) - the domain of model based analysis of biological processes and function.

If well-conceived, such enabling KC structures will rebuild the structures of innovation for the Life Sciences, and thereby transform key sectors of society. This requires that scientists also align their work of building research infrastructures with societal activities and matters of concern. We need inovative research approaches that utilise the powers of KC structures and in addition take responsibility for societal ramifications.

Such approaches are currently referred to as **Responsible Research and Innovation (RRI)** . The project will reflect on its own work in order to identify and assess key societal concerns emerging in innovation systems that have the potential to transform medicine.

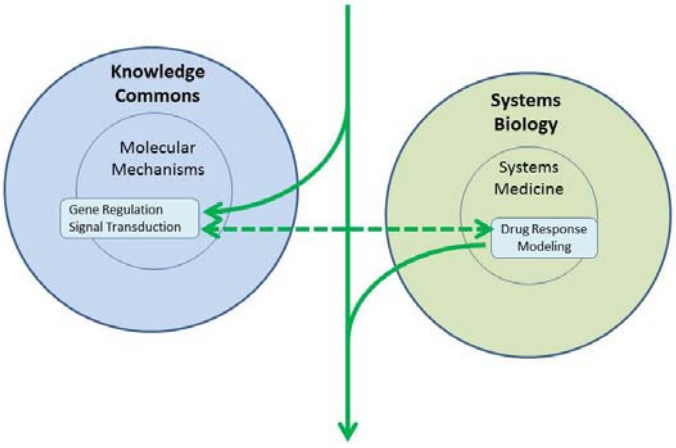

Figure 2: Interlinked Knowledge Commons and Systems Biology

The DrugLogics project particularly focuses on the Knowledge Commons of Gene Regulation and Signal Transduction, to enable Drug Response modelling within Systems Medicine research for Presicion Oncology. The assembly of models is dependent on prior knowledge, most explicitly biological components and their pathway interactions (in the form of mathematical formulas or logical relationships).

Subprojects

The DrugLogics initiative comprises a number of different subprojects, all geared towards the development of *personalised medicine*, or *precision medicine*.
In the subproject '**Crossover Research 2.0 – Well constructed Knowledge Commons'** (www.ntnu.edu/crossover-research) the domain of precision medicine is explored as a key visionary driver for developing the Knowledge Commons and the enabling of Systems Biology approaches to innovate health care. In particular, we seek to engage stakeholder concerns in investigating and establishing strategies for DrugLogics to contribute to the Knowledge Commons in an RRI mode.

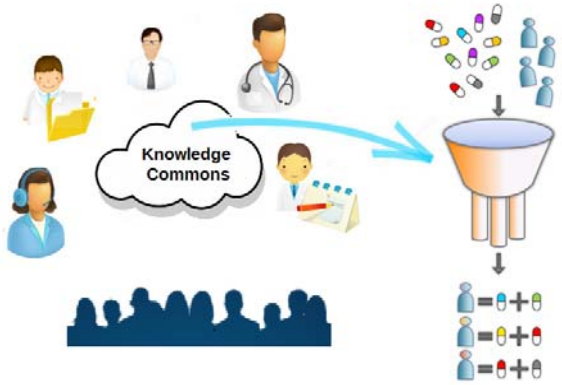

Figure 3: Knowledge commons in precision medicine built on Resposible Research and Innovation

The subproject **'Rational development of anti-cancer combinations'** focuses on precision medicine for cancer by pursuing novel insight into cancer disease mechanisms, combinatorial drug treatment in order to enable selection of the best treatment for the individual patient. The aim is to develop and integrate computational, experimental and analytical approaches to predict and validate anti-cancer drug combinations and produce an integrated pipeline for rational screening of synergistic drugs and for clinical decision support in precision medicine.
In the subproject **'Using computer models to predict drug resistance in colon cancer'** (www.colosys.org) we will develop a deeper understanding of colon cancer networks and convert them into computer models with which we will be better capable to predict response to treatment. The combination of computational, experimental and clinical testing will be explored to understand drug resistance mechanisms, further paving the way towards personalised treatment of colon cancer.
These three different subprojects require a multidisciplinary skill base, and we build on collaboration that has been ongoing for over 10 years during which we developed skills and personal relationships that significantly capacitate us in pursuing this kind of research.

Figure 4: Joint aim of multidisciplinary fields

Our mode of integrative collaborative work is symmetrical[1], i.e. we aim at creating research venues where each project participant can contribute to joint aims in ways that at the same time allows researchers to advance the state-of-the-art in their respective disciplinary fields. This mode of working can contribute to increase the relevance and enabling capacity of systems biology research, e.g. by addressing computational problems that arise in the border zones between the different disciplines involved. This approach can therefore also be instrumental to take responsibility for social ramifications as we identify such border zones as key venues for systems biology-induced transformations that need to be responsibly modulated. We simultaneously address issues of *doability* and *desirability* as we identify, trace and evaluate normative drivers, paying attention to how epistemic and ethico-political quality measures cross-over in the construction of KC infrastructures.

[1] **Nydal,R**, Efstathiou, S and **Lægreid, A**. (2012) Crossover Research: Exploring a collaborative mode of integration, In van Lente H et.al Little by Little. Expansions of Nanoscience and Emerging Technologies 181-194

Short term and long term Challenges

Development of precision medicine is often legitimised as a proper response both to societal challenges like efficiency, sustainability and equity of health care systems[2], and to scientific challenges related to the immense diversity of diseases caused by large variation between individuals. The vision of precision medicine is a powerful motor for developmenting novel research infrastructures as it connects and mobilises societal and scientific expectations and concerns, in particular in the case of cancer. Cancer ranks among the leading causes of death, with an expected 40% worldwide rise by 2025[3], and new scientific understanding of inter-tumour heterogeneity makes oncology a clear choice for precision medicine[4]. For many patients standard treatment is inadequate due to individual variation in drug efficacy, adverse drug side effects, and development of drug resistance. Combinatorial drug treatment tailored to the individual tumour is expected to overcome many of these problems, but our knowledge about such beneficial drug combinations is still limited.

Precision medicine relies on coordinated collective action. In the case of tailored drug combinations, clinicians would eventually need to have advanced decision support systems at hand that can underpin the choice of (combination) treatment. These systems should assist the interpretation of patient data, increasingly provided by omics technologies that produce 'big data' that all need to be analysed in an integrated manner. In particular, as is a project focus, these systems can gain significantly more power if they are informed by a 'Knowledge Commons', which represents the aggregation of all relevant scientific knowledge.

The long term vision of precision medicine is contingent on extensive research infrastructures that need to be constructed, validated and adjusted to meet both short term and long term research goals. The work of building infrastructures of the future therefore needs to be anticipatory, inclusive and responsive to emerging social and material conditions and matters of concerns. Challenges that need to be overcome in order to enable precision oncology are related to:

- building and application of the Knowledge Commons for computational tumour model generation, patient data interpretation and clinical decision support.
- design and deployment of experimental systems for the identification of beneficial drug combinations,
- assessment of biomarker and clinical information for choice of treatment (companion diagnostics), development of predictive computational tumour modelling that will allow testing of only the most promising drug candidates.

Predictive computational models that can reliably simulate the effect of drug combinations for individual tumours can rationalise the pre-selection of potentially effective combinations and reduce the huge experimental search space, or, conversely, identify combinations that need not be tested because they likely have no beneficial effect[5]. Initial proof of the feasibility of predictive modelling of drug response has been reported[6,7] and was also achieved by us[8]. To be applicable for large repertoires of cancer models a modelling platform will need further improvement of mathematical and computational methodology for semi-automated model generation.

The assembly of models accurately depicting cancer cell decision-making networks needs knowledge about biological system components and how they interact. This background knowledge resource needs to be

[2] http://ec.europa.eu/research/participants/data/ref/h2020/wp/2014_2015/main/h2020-wp1415-health_en.pdf
[3] http://www.cancer.gov/aboutnci/budget_planning_leg/plan-archives/NCIs-Annual-Plan-Budget-Proposal-Fiscal-Year-2016.pdf
[4] Collins FS, Varmus H. A new initiative on precision medicine.N Engl J Med. 2015 Feb 26;372(9):793-5
[5] Doudican NA, et al. Personalization of cancer treatment using predictive simulation.*J Transl Med*. 13(1):43. 2015 bPMID: 25638213
[6] Bansal M, et al. A community computational challenge to predict the activity of pairs of compounds.; *Nat Biotechnol* 32:1213. 2014;
[7] Crystal AS, et al. Patient-derived models of acquired resistance can identify effective drug combinations for cancer. *Science*. 2014; 1–
[8] Flobak Å, Baudot A, Remy E **Thommesen L**, **Thieffry D, Kuiper M, Lægreid A** Discovery of Drug Synergies in Gastric Cancer Cells Predicted by Logical Modeling. *PLoS Computational Biology*, manuscript in review 2015

designed as a life science 'Knowledge Commons': the freely available, open sourced, quality assured (and verifiable) resource of facts, information and knowledge about biological parts or components, their relationship in systems, and their use in models to describe biology and explain data[9,10].

Designing and building infrastructures for the Knowledge Commons is furthermore needed to rationalise the analysis of existing big data, and even more challenging, to build bottom-up knowledge-based research structures to *manage* and *engineer* knowledge in ways that enable precision medicine[11]. KC design and construction work therefore needs to be inspired by a broad range of stakeholders, potential data and knowledge providers, and a variety of end-users. Moreover, such structures should not only be comprehensive in terms of the number of involved institutions and professional activities, but also require novel ways of analysing and optimising the sharing of knowledge bases in such ways that they can seamlessly underpin analysis of data with different types of analysis objectives, confidentiality issues, and applicational practices.

Objectives

Our overall objective is to investigate and demonstrate how Systems Medicine can deliver a well-constructed pipeline for rational screening for synergistic drug combinations and a foundation for clinical decision making for anti-cancer combination therapies under the precision oncology vision.

Our specific aims are to show that computer models of cancer cells can be:

- automatically built if supported by an adequate source of biological knowledge, also named Knowledge Commons, a freely available resource of information about how proteins and other molecules in a cell together regulate biological processes (causal statements);
- tailored to represent very specific cancer cells and tumours by use of molecular information of the particular cancer, or even general patient biomarkers;
- used to identify the molecular mechanisms crucial to cancer progression
- used in multiscale approaches to predict the response of cancer cells to drugs and drug combinations
- supported through systematic scrutiny of epistemic and ethical-political conditions for well-constructed innovation systems for precision oncology.

Our multidisciplinary team involving researchers from the humanities, sciences and medicine will assess how research can enable not only a doable, but also a responsible, reflective and responsive innovation process for the Knowledge Commons, and thereby provide a key component for precision medicine

[9] Good BM, et al Organizing knowledge to enable personalization of medicine in cancer. *Genome Biol*. 15:438, 2014
[10] **Lægreid A, Kuiper M**. Health and the information commons. *Pan Eur Networks: Government*, 13: 144; 2015
[11] Cases, Montserrat, et al. Improving data and knowledge management to better integrate health care and research. *JInt Med* 274 (2013): 321

Planned work

In our joint work we will:

- design a prototype Knowledge Commons that underpins computational simulations for precise and individual diagnosis and treatment of cancer
- contribute to the Knowledge Commons by developing a high-quality, low-noise repository of causal statements that can be used as building blocks for cell-fate decision networks relevant to model disease mechanisms of specific cancers
- identify cancer biomarker data necessary for understanding the patient-specific configuration of the network that drives a particular cancer, either from new or existing (public) data from cancer biobanks
- develop automated building and refinement of logical (Boolean) models from causal statements tailored to specific cancer cells using their biomarker data and use these models to predict the effects of drugs singly or in sets on these specific cancer cells
- test computationally generated predictions in cancer cell cultures in a high throughput manner enabled by robotic screening facilities
- test promising sets of drugs in clinically relevant cancer models like mouse xenografts
- support the design of a prototype for Knowledge Commons by developing and implementing a strategy for a Responsible Research and Innovation (RRI) mode of working.
- map the innovation system for the precision medicine research infrastructure, including knowledge commons infrastructures as a starting point for our RRI strategy, aming to identify key scientific and social bottlenecles and the responsibility challenges they pose.
- engage a broad stakeholder base to help identify normative drivers and scientific constraints, clarify available choices and anticiptate ramifications of these choices.
- investigate how our RRI strategy support scientific solutions, including its ability to withstand trials of moral engagement and scrutiny as we critically evaluate the limitations and possibilities of our proposed method.

Background – some elements that we build on

Combinatorial anti-cancer treatment, model-based prediction to guide preclinical testing

Development of efficient combinatorial anti-cancer treatment

Combined anti-cancer drugs may together target multiple robustness or weakness features of specific cancer subgroups or individual tumours[12], and their effectiveness can be further enhanced by exploiting synergistic drug actions that inhibit cancer growth and evade tumour resistance mechanisms more efficiently than drugs administered individually. Synergistic combinations also allow for a significant reduction in the dosage of individual drugs while retaining the desired effect, and thereby can ensure treatment efficacy without pushing single drug dosage to levels inducing adverse effects.

Modelling to guide preclinical pipelines for identification of combinatorial treatments

Originally spearheaded by S. Kauffmann[13] and R. Thomas[14], logical (Boolean) multiscale models have been shown to accurately describe molecular mechanisms underlying cellular decision making[15]. Boolean models can be hand-built from logical statements that are derived from pathway databases, general knowledge bases and the scientific literature. The correctness of models can be checked by observing that logical rules during a simulation/model updating scheme govern model state transitions that evolve to a stable state (or cycle), representing a clearly definable biological or cellular state. Many Boolean modelling software tools are available for this, and some have been used by us, in particular the software suite GINsim[16] which we have used to build an extensive logical multiscale model for the cancer cell line AGS[10]. Starting with a regulatory network valid for a variety of cells and conditions, the model was configured with baseline phenotypic biomarkers from actively growing AGS cells to obtain a 'committed model' accurately depicting the regulatory logics of AGS cells and connecting it to the phenotype scale. After model reduction done to improve the computational tractability, batch-wise simulations emulating a combinatorial drug perturbation strategy predicted five synergistic drug combinations from a total of 21. Experimental testing of all drug combinations for their effect on AGS cell growth confirmed four of the five combinations synergistically reducing cell growth, indicating a false positive rate of only 20%. Importantly, the predictions did not suffer from false negatives indicating the efficacy of this approach to eliminate non-effective combinations without preventing potential blockbuster drug combinations from being tested. This is a key requirement for any *in silico* screening strategy. Our approach is therefore relevant to preclinical discovery of efficient anti-cancer drug combinations, and thus for the development of strategies to tailor treatment to individual cancer patients.

Knowledge for models depicting regulatory networks guiding cancer cell decision

[12] Al-Lazikani et al Combinatorial drug therapy for cancer in the post-genomic era. *Nat Biotechnol* 30: 679–, 2012
[13] Kauffman S. Homeostasis and differentiation in random genetic control networks. Nature 1969, 224:177–8.
[14] Thomas R. Boolean formalisation of genetic control circuits. J Theor Biol 1973, 42:565–583.
[15] Wolkenhauer O. *Front Physiol*. 5:21. 2014. PMID: 24478728; Wolkenhauer O, et al..*Genome Med.* 26:21-, 2014. PMID: 25031615
[16] Naldi A, Remy E, **Thieffry D**, Chaouiya C. Dynamically consistent reduction of logical regulatory graphs. *Theor Comput Sci.* 2011;412: 2207-, 2011; Grieco L, Calzone L, …, **Thieffry D**. Integrative modelling of the influence of MAPK network on cancer cell fate decision. Miyano S, editor. *PLoS Comput Biol*. 9: e1003286-, 2013

Background knowledge sources, pathways, regulatory networks, causal reasoning:

The amount of biology that can be explained without the use of models is shrinking[17], Automated model assembly seems straightforward, as many knowledge bases in the public domain (e.g. Reactome (http://www.reactome.org/) and Pathway Commons (www.pathwaycommons.org/)) contain detailed information about biological networks and pathways, and their components and relationships. For logical modelling, however, the only essential relationships are those that indicate causality: relationships between network nodes (proteins, RNAs, genes) that carry information about regulation - molecular actions that activate or inactivate another molecular component in a network. These causality statements can be obtained from pathway resources mentioned above, from structured databases like SIGNOR, or from the literature, assisted through text mining efforts.Although many efforts are ongoing to accumulate and curate these types of knowledge, additional efforts are needed, for instance on the curation of DNA binding transcription factors and on signal transduction pathway components (refs). Central to this effort will be the CNIO-NTNU-collaborative research on text-mining based information retrieval of causal statements from literature[18] building on the strong competence in literature information retrieval of the Valencia group[19].

Biomarker data: Genotype and phenotype information on cancer cell lines, patient-derived xenografts, patient data from solid and liquid biopsies and other tumour material

Thus, phenotype information (e.g. transcriptomic or cell signaling status) will be necessary to provide additional input for the development and deployment of combinatorial anti-cancer treatment[5] and for the foreseen necessary movement from druggable targets to druggable (sub)networks[27]. Indeed, the accuracy of predictive modeling of drug combination effects in pre-clinical cancer cell line models was crucially dependent on phenotype (transcriptomic) data[20].
The wealth of publicly available data for gaining insight into regulatory networks that drive cancer includes cancer omics available through TCGA- and ICGC-portals which provide genomics (genome-/exome sequence, copy number aberrations), epigenomics (mainly DNA methylation), transcriptomics and proteomics (mainly RPPA, reverse phase protein array); cancer cell line drug responses available from e.g. the CCLE project; and data on genetic vulnerabilities affecting cancer cell line viability, determined by genetic perturbation reagents (shRNAs or CRIPR/Cas9) to silence or knock-out individual genes from the Achilles project[21].

Multidisciplinary integration for Resposible Research and Innovation (RRI)

The innovative and transformative powers of science can be studied in terms of how actions are mediated through the field's experimental systems. In Rheinberger's words, an experimental system is the smallest working unit designed to give unknown answers to questions that the experimenters are not yet able clearly to ask. The process of constructing these systems is governed by an internal dynamics, what Hacking described as the "self-vindicating" dynamics of laboratory research. Scientific work, when succeeding, may be

[17] Green, S., & Wolkenhauer, O. (2012). Integration in action. *EMBO reports*, 13(9), 769-771.
[18] Leitner F, Krallinger M, Tripathi S, **Kuiper M, Lægreid A, Valencia A**. Mining cis-Regulatory Transcription Networks from Literature. Proceedings of *BioLINK*, ISMB/ECCB SIG 2013
[19] Leitner F, et al *Nat Biotechnol.* 2010 28:897-. PMID: 20829821; Salgado D, et al .*Bioinformatics*. 2012, 28:2285- PMID: 22789588
[20] Bansal M, et al. . A community comp. challenge to predict the activity of pairs of compounds. *Nat Biotechnol* 32:1213-, 2014
[21] **TCGA**: http://cancergenome.nih.gov/; **ICGC**: https://dcc.icgc.org/); **CCLE** (http://www.broadinstitute.org/ccle; **Achilles**: http://www.broadinstitute.org/achilles

controversial as it involves building machineries for creating common futures, which is particularly evident in large experimental systems built to enable innovation.[22]

The notion of experimental systems identifies the task of RRI research initiatives in the context of the need to "rethink science", or the call for "new social contracts".[23] A conceptual and institutional ideals of clear separation between scientific and societal activities that have governed professional divisions of labour. These orders have been identified and discussed in terms of the "social contract" between science and society, ideals that have been argued as necessary to be reconsidered in light of what science has become.[24]

The smalles working units of science is no longer easily confined to a laboratory or a research group, like exemplified in the work needed to build research infrastructures enabling innovations pathways for precition oncology.The prototype system engineered in the project provide a platform for they study of enabling innovation systems of the future. The hallmark of experimental sciences can be seen as the one of creating orders or "stability"[25]. Such stable or reliable orders is arguably in large research structures more evidently crossing over the natural and the social, often referred to as "socio-technical" orders. Building such orders is now also explicitly expressed as goals of large scale scientific initiatives (typically labelled as *enabling* or *converging* technologies). RRI/ELSA initiatives emerged in the context of such priority areas where changes in modern science are particularly evident (widely discussed as shifts from normal to "post-normal", academic to "post-academic" or Mode 1 to "Mode2" science). RRI initiatives reflect how scientific activities are seen to be a collective social concern as they perform "collective experiments" on our common futures, that in turn call rethinking ways to coordinate scientific, industrial and societal efforts. [26]

RRI activities are widely recognised as urgently needed, despite of few generally recognised success stories and lack of unifying analysis across sectors of the why's and how's of RRI. State-of-the-art RRI actions are basically still at a stage of outlines of frameworks and definitions.[27] In our analysis, the work of restructuring *normative* orders are critically challenging for RRI initiatives. The challenge of RRI thus needs to be understood in terms of how professional identities and goals are challenged. The very understanding of the ethos of one's professional practice includes how it is to be conducted well in relation to other adjacent practices. Integrated projects appear to us as one, among many, important RRI approaches as they provide an important venue for engaging the ethos of collectives as well as constituent fields of practitioners.

[22] Hacking,I. 1992 The Self-Vindication of the Laboratory Sciences. In Pickering 1992 (ed.) *Science as Practice and Culture*. - Rheinberger, H-J.1997 *Toward a History of Epistemic Things* - Rabinow,P.et.al.2005 *A Machine to make a future*.

[23] Nydal,R.2005 *Rethinking the topoi of normativity.* Phil. dissertation, NTNU - Nowtny, H. et.al.2001 *Re-thinking science*

[24] Winner, L. 1993 A New Social Contract for Science. *Technology Review* (96) 65. - Lubchenco, J. 1997 Entering the Century of the Environment: A New Social Contract for Science. *Science* (279) 491. - Guston, D. H. and Keniston, K. 1994 Updating the Social Contract for Science. *Technology Review* (97) 60. - Gibbons, M. 1999 Science's New Social Contract With Society. *Nature* (402) 81.

[25] Fujimura, J. H. 1996. *Crafting Science*. Galison, P. 1987. *How Experiments End.* Pickering, A. 1995 *The Mangle of Practice*. Rheinberger, H-J. 1997. *Toward a History of Epistemic Things*. Knorr-Cetina, K. 1999 *Epistemic Cultures*

[26] Latour, B 2004 "Which protocol for the new collective expeiments?" In Schmindgen,H. (ed) *Experimental cultures European Commission reports a) Nordmann A. 2004 Converging Technologies - Shaping the Future of Euopean Societies.b)Hoven J 2013 Options for streghtening responsible research and innovation.* Latour, B. 2004 *The Politics of Nature*.

[27] Rip, A.; Schot, J.W.; Misa, T.J. 1995 *Managing Technology in Society. The Approach of Constructive Technology Assessment* - Guston, D, og Sarewitz, D. 2001 Real-time technology assessment. *Science and Public Policy* (33) 5-16, 2001 - Conferansen I rom, Rip, RRI boken