



REVIEW REPORT OF FP6 PROJECTS

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Individual report
Consolidated report

Thematic Priority/Activity

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Instrument type

Integrated Project

Project no and acronym

LSHC-CT-2003-506803
INTACT

Project full title

Identification of Novel Targets for Cancer Therapy

Project start date

1.1.2004

Project duration

4 years

Project coordinator name and
organisation

Kristian Helin
University of Copenhagen (UKBH)

Period covered by report
(from - to)

1.1.2006 - 31.12.2006

Date of (review) meeting

31.1.2007 - 2.2.2007

Name(s) of reviewer(s)

Peter DANIEL

Name of reviewer drafting
the report

Peter DANIEL

1. OVERALL ASSESSMENT

a. Executive summary

Please follow the order of the individual sections of this report

Comments:

The first and most relevant aim of the project is to develop and apply large-scale functional genomic screens by the use of shRNA libraries to achieve a loss-of-function in the investigated cancer models via RNA interference (RNAi). This has led, as planned, to the identification of several candidate genes, some of them acting in epigenetic regulation of malignant transformation, especially in myc-driven transformation. This aim has been met very well and a number of high ranking publications and patents are going to result from these productive efforts. Nevertheless, the partners apply very different technologies to their RNAi screens. Instead of using a single technology, multiple parallel developments are being pursued. This is in part due to the fact and technical problem that the human shRNA library was not validated by sequencing so far. This problem should, however, be solved towards the end of the funding period as sequencing of the human library is under way by help of the Sanger Center (UK).

Another less-productive part of the work programme is the development of the "living cell micorarray" propagated by the partner IEO2 (Pellicci). Nevertheless, this shortcoming has been very well compensated by contingency efforts of the consortium to apply selection screens in microwell plates. This has led, as mentioned, to the identification of a significant number of candidate genes that are now evaluated as putative target genes for experimental cancer therapy. In addition to these RNA interference screens and based on the identified candidate genes, novel anticancer drugs are planned to be developed in collaboration with the hungarian SME Vichem. There is considerable concern regarding this part of the project.

Due to unforeseen events and the termination of the SME Morphochem, another SME has joined the team: Agendia. This company is specialised on genome wide expression profiling and has started to apply this technology to the consortium. At the time of the review meeting in Copenhagen in early 2007, Agendia had performed a gene expression profiling effort in non-small cell lung cancer patients with progress in another cancer entity, breast cancer and plans to analyse lymphoma samples as well. Data presentation was very preliminary and it was not possible to see a direct link between these efforts and the functional genomic screens performed by the academic partners of the consortium. Comparative insights from different tumor entities and the functional genomic RNAi screens were lacking at the time of the review meeting. Albeit the work of Agendia is very well estimated in the field of expression profiling in cancer, the evidence for a true collaborative relevance to the aims of the consortium did not become sufficiently evident.

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|-------------------------------------|---|
| <input type="checkbox"/> | Good to excellent project (The project has fully achieved its objectives and technical goals for the period and has even exceeded expectations) |
| <input checked="" type="checkbox"/> | Acceptable project (The project has achieved most of its objectives and technical goals for the period with relatively minor deviations) |
| <input type="checkbox"/> | Unsatisfactory project (The project has failed to achieve critical objectives and/or is not at all on schedule) |

b. Recommendations

As mentioned in the executive summary, most academic projects are on track.

This is not the case for technologically very demanding living cell microarray approach of WP4 (IEO2, Pellicci). Nevertheless, an updated but probably too ambitious work programme that addresses the technological issues with alternative strategies has been submitted. While I do not believe that the whole work package can be completed in the projected time frame, I would still expect to see proof-of-concept results by the end of the funding period. In contrast, WP13 is developed very adequately and very productively by partner IEO2.

The two other weak points refer to the SME partners Vichem and Agendia.

In case of Agendia, a very strong effort must be put on the direct linking of the expression profiling work in the different tumor entities (non-small cell lung cancer, breast carcinoma, lymphoma etc.) to the results obtained so far in the RNAi screens of the academic partners. As it stands, the work of Agendia done so far is more or less unrelated to the functional genomics work of the consortium. This could, however, be overcome but a major and convincing effort would be required to relate the expression profiling activities by Agendia to the work being done by the academic partners.

In case of Vichem, the efforts to identify tumor specific small molecule compounds in synthetic lethal screens was not very productive so far. The plan to screen c-myc overexpressing cells was abandoned without satisfactory explanation and the focus was then on p53 deficiency. Screening is based on the small nested chemical library based on kinase inhibitor core structures and was performed in the HCT116 cell line system where an isogenic, biallelically p53 deleted subline is available. Overall, this work is very simplistic and lacks interaction with the network partners. This apparent lack of interaction that is reflected e.g. by the lack of use of the proprietary cell line systems available in academic labs of the consortium that could be employed for the identification of drugs targeting p53 deficient cancer cells. Of note, the p53 deficient HCT116 system was developed by Bert Vogelstein, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University. Its unlicensed use for drug development is problematic and prone to litigation of intellectual property generated by the use of this cell system.

2. OBJECTIVES

a. Have the objectives for the period been achieved?

☐
Yes

☒
Partially

☐
No

Comments:

Objectives of the academic partners were overall met within a margin of expected technical problems and contingency strategies. This does not apply for WP13 and the WPs of the SMEs Vichem and Agendia as detailed above. As known, the SME Morphochem dropped out of the consortium and therefore the associated WPs and objectives could not be met.

b. Are the overall objectives (i) still relevant and (ii) still achievable within the time and resources available to the project?

(i)
☒
Yes

☐
Partially

☐
No

(ii)
☐
Yes

☒
Partially

☐
No

Comments:

The SMEs should make a major effort to interact more closely with the academic partners.

This applies not only for Vichem that is not following the original plan to study synthetic lethality induced by their small molecules in myc overexpressing cells. Of note, the p53 work they perform now does make per se sense but the level of technology is far too simplistic, especially with regard to the cell line model they utilize. Technological input and use of additional cell line models from the consortium is urgently required. If the work remains on this level of technology the results are going to be anecdotal and useless.

Work done by Agendia should also more closely interconnect with the functional genomics projects. Their results should be employed to guide the expression profiling analyses to study gene expression profiles in 3 tumor entities (lung and breast cancer and lymphoma). They closely follow the work plan of the draft planning from february 2006 and therefore fulfill their contractual obligations but this could clearly be done better and more enthusiastically, especially in a closer interaction with the RNAi screen projects.

As it stands, both Vichem and even more Agendia are performing work that they would have done probably anyway, even without funding by the INTACT project. In case of Agendia, their work is in accordance with the draft planning as of february 2006. This is not the case for Vichem.

c. Do you recommend changes in objectives in order to keep up with the current state-of-the-art?

☐
Yes

☒
Partially

☒
No

Comments:

Especially Agendia should try to connect the functional genomics results to the expression profiling data they have generated.

3. WORKPLAN AND RESOURCES

a. Has the project as a whole been making satisfactory progress in relation to the Description of Work (Annex I to the contract)?

☒
Yes

☐
Partially

☐
No

Comments:

Interaction with the SMEs is not satisfactory. This affects application and dissemination of the functional genomics results from the RNAi screens.

b. Has each work package (WP) been making satisfactory progress in relation to the Description of Work (Annex I to the contract)?

☐
Yes

☒
Partially

☐
No

Comments:

This applies to WP13 (living cell microarray, partner IE02) and the WPs by the 2 SMEs as detailed above.

c. Have planned milestones and deliverables been achieved for the reporting period?

☐
Yes

☒
Partially

☐
No

Comments:

See above.

d. Have resources been deployed as foreseen in Annex I, overall and for each participant?

☐
Yes

☒
Partially

☐
No

Comments:

Changes occurred due to contingency planning. These are in my view acceptable.

e. Have costs incurred (personnel costs and other major cost items) been 1) necessary for the implementation of the project and 2) economic. Note that both aspects (1 and 2) have to be covered in the answer.

☐

Yes

☐

Partially

☐

No

Comments:

f. For Networks of Excellence (NoEs) only:

Is there evidence of real integration and restructuring of activities between partners (to be evaluated against Indicators of Integration, e.g., exchanges of personnel, shared infrastructures, joint research and training activities, changes of research orientation of individual partners to better integrate into the NoE, etc).

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

4. WORK PLANNED FOR THE NEXT 18-MONTH PERIOD (NoEs and IPs only)

Is the proposed update to the Implementation Plan (IPs) or Joint Programme of Activity (NoEs) for the next 18-month period satisfactory

a. from a scientific/technical point of view?

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

b. from a management point of view including use of resources?

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

c. concerning non-scientific activities (dissemination, exploitation, training, science-society issues, further integration etc)?

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

5. CONSORTIUM PARTNERSHIP

a. Has the collaboration between the participants been effective?

☐
Yes

☒
Partially

☐
No

Comments:

Interaction between the SMEs and the academic partners is insufficient. Use of parallel approaches for RNAi (different libraries) is not satisfactory but occurred in consequence of technological problems. Use of a single library would have yielded more comparable results.

b. Have the partners contributed as planned to the project and tasks assigned to them?

☐
Yes

☒
Partially

☐
No

Comments:

Results presented by Vichem are not related to the RNAi screen results and the myc related work plan was simply skipped. The p53 related work of Vichem is too simplistic and I would be very surprised to see results that would open new perspectives for targeted cancer therapy based on p53-deficiency associated synthetic lethality.

c. Do you identify any conflicts or evidence of underperforming partners, lack of commitment or change of interest of any partners? Do you recommend any changes in responsibilities?

☐
Yes

☒
Partially

☐
No

Comments:

See above for comments relating to Vichem and Agendia.

6. MANAGEMENT

a. Has the scientific/technical management been performed as required?

☒
Yes

☐
Partially

☐
No

Comments:

Members of the SAB were present at the Copenhagen meeting. SAB activities could not be assessed and seem to be rather limited.

b. Has the administrative and financial management been performed as required ((including proper handling of contractual matters, maintenance of the consortium agreement, intellectual property rights, technical collective responsibility, sub-contracting, competitive calls)?

☒
Yes

☐
Partially

☐
No

Comments:

As far as it is possible to perceive.

c. Have (electronic) information and communication networks been established as required to support interactive working between the teams involved (if relevant)?

☒
Yes

☐
Partially

☐
No

Comments:

Communication between the academic partners is excellent. Communication with the SMEs and data access should be improved.

d. Is the consortium interacting in a satisfactory manner with other related 5th and 6th Framework projects or other R&D national/international programmes (if relevant)?

☐
Yes

☐
Partially

☐
No

Comments:

No data available.

7. USE AND DISSEMINATION OF KNOWLEDGE

a. Does the project have significant use potential (if applicable)?

☒

Yes

☐

Partially

☐

No

Comments:

The academic partners are outperforming. Several publications with probably high impact are in preparation. Applicability of the shRNA libraries, once available, is very high. If progress continues in this pace, I foresee a major problem of preclinical/clinical application due to limitations in the interaction with the SMEs.

b. Is the Plan for the Use and Dissemination of Knowledge developing in a satisfactory manner?

☐

Yes

☒

Partially

☐

No

Comments:

See above

c. Have the contractors disseminated project results and information as foreseen by the contract and the plan for dissemination and use of knowledge (publications, conferences...)?

☒

Yes

☐

Partially

☐

No

Comments:

Publication activities and perspectives are excellent. Conference participation and data presentation is very active.

d. Are potential users and other stakeholders (outside the consortium) suitably involved (if applicable)?

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

8. OTHER ISSUES

a. Have policy-related and/or regulatory issues been properly handled (if applicable)?

☒

Yes

☐

Partially

☐

No

Comments:

b. Have ethical issues been appropriately handled (if applicable)?

☒

Yes

☐

Partially

☐

No

Comments:

c. Have safety issues been properly handled (if applicable)?

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

d. Has progress on the Gender Action Plan been satisfactory (if applicable for this reporting period)?

☐

Yes

☐

Partially

☐

No

Comments:

n.a.

Name (s) of the reviewer(s): Peter DANIEL

Date: 5.10.207

Signature(s):

