The use of objective oriented project planning tools for nanosafety and health concerns: A case study in nanomedicine research project

Article *in* European Journal of Nanomedicine · January 2016

DOI: 10.1515/ejnm-2015-0050

5 authors, including:

Mohammad Reza Nejadmoghaddam
Avicenna Research Institute

Abdolreza Babamahmoodi
Shahid Beheshti University of Medical Sciences

Rassoul Dinarvand
Tehran University of Medical Sciences

Short Communication

Mohammad-Reza Nejadmoghaddam, Abdolreza Babamahmoodi, Arash Minai-Tehrani, Amir-Hassan Zarnani and Rassoul Dinarvand*

The use of objective oriented project planning tools for nanosafety and health concerns: a case study in nanomedicine research project

DOI 10.1515/ejnm-2015-0050
Received December 10, 2015; accepted June 20, 2016; previously published online August 6, 2016

Abstract: Potential human health and environmental risks associated with nanoscience research projects and their deliverables, termed nanosafety, is one of the important issues for translating research findings into commercially viable products. This paper examined the applicability of project management tools to address nanosafety in an efficient manner. Using objectives oriented project planning (OOPP) we describe a new integrated content of the problem tree, the result tree, and the logical framework approach (LFA), by modeling our nanomedicine research project entitled “Nanomedicine preparation based on antibody drug conjugate (ADC)” as a case study. As a main result of the case study, we demonstrated an LFA matrix that highlights the need to deal with nanosafety as an activity of the research project. Consequently, the activity can lead to the output, standing operating procedure (SOP), for managing the project waste disposals and its deliverables side effects. In general, such output can be concluded as an important output for all nanoscience research projects to avoid underestimating risks for their nano-objects. Moreover, this article is written in the hope of providing an easy-to-understand template of project management tools for novice nanomedicine researchers who aim to apply OOPP in the design of their research projects.

Keywords: antibody drug conjugate (ADC); nanomedicine research project; nanosafety; project management tools; translational steps.

***Corresponding author: Rassoul Dinarvand,** Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS), P.O. Box 14155-6451, Tehran, Iran; and Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS), P.O. Box 14155-6451, Tehran, Iran,
Phone: +982164121125, Fax: +982122432021,
E-mail: dinarvand@tums.ac.ir
Mohammad-Reza Nejadmoghaddam: Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS), P.O. Box 14155-6451, Tehran, Iran; and Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran
Abdolreza Babamahmoodi: Health Management Research Center, Baqiyatallah University of Medical Science, Tehran, Iran
Arash Minai-Tehrani and Amir-Hassan Zarnani: Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran

Background

Nanotechnology has demonstrated dramatic progress in the medical application called nanomedicine (1). Nanomedicine is an interdisciplinary research approach to assist the improvement of therapeutic and diagnostic methods by increasing efficiency, safety and patient compliance, eventually keeping health care expenditure low and contributing to the economy (2–4). Work on nanomedicine research projects has gained significant interest in universities and research centers. For example, the tumor-targeted nanomedicines research that would target specific sites in the body account for 76% of publications and 59% of patents, in the past few years (5, 6). Regardless of the impressive numbers of publications and patents, the real success, of nanomedicines, like of any other emerging technologies, depends on translation into application (3, 6–9). To this end, like other nanoscience projects, one of the main translational challenges is compliance with regulations for nanosafety (5, 10, 11). This pertains to the entire life cycle, including disposal of waste produced during production, and the highly complex interactions of nanostructures with the ecosphere, in particular in natural reservoirs (3, 7, 12–18).

A number of approvals for environmental risk assessment are required to complete the transition from nanomedicine product design to the market (10). To obtain the approvals, many research-funding programs and regulations strongly suggest the use of professional project management methods to plan research projects and applications for market authorization (19).

In this content, objectives oriented project planning (OOPP) methodology and in particular the logical framework approach (LFA) are considered very practical methods for research management, due to their inherent flexibility regarding the specific way towards the fulfilment of objectives (20, 21). The LFA is a standard part of the project management body of knowledge (PMBOK) portfolio (22). It is predominantly a frame of reference to structure the dialog among project planners to achieve a clear vision of the project's activities, outputs, outcomes, and impacts (20, 21, 23–25).

The aim of our study is to examine the capability of OOPP and LFA to analyze potential safety issues in the planning of emerging technology projects while providing effective solutions. In particular we aim to introduce the OOPP as a practical tool for novice researchers involved in the design of nanomedical development (26, 27). For this purpose, we used the LFA to design our research project "Nanomedicine preparation based on antibody drug conjugate (ADC)" as a case study in nanomedicine research projects. The concept of an ADC is, employing an antibody to deliver a highly chemocytotoxic agent specifically to the selected tumor cells with minimal impact on healthy cells. This approach is currently a major focus of research on antibody-based cancer therapy and a promising new treatment option for cancer patients (28–31). Antibody drug conjugates (ADCs) have been introduced as a promising tumor-targeted nanomedicine to solve the low clinical activity problems related to conventional chemotherapy, naked antibodies and combined strategies (30–32). The use of ADCs as small molecule therapeutics meets the concepts of tumor-targeted nanomedicines including: being controlled at the nanometer scale (antibody acts as a natural/biological nanocarrier), evading the immune system, site-specific targeting, controlled release, and minimal side effects (9, 33, 34). In the ADC project we had to consider several issues such as choosing an appropriate antibody targeting specific tumor, finding a highly potent cytotoxic agent and selecting a suitable strategy for the linkage of the cytotoxic agent to the antibody. This highlights the complexity of the project; it further motivates the use of a modern management system to design the project.

Methods

Using objectives oriented project planning (OOPP), the following steps were taken to achieve the logical framework (or logframe) matrix.

Project analysis phases

LFA is a helpful tool for project design, approval, and evaluation through its compatibility to integrate with other project management tools. In this regard, LFA integrates the problem tree and the result tree, putting key objectives in the center (25, 35). This integration provides a practical way to detect hidden problems, underestimated given risks, black swans, and weak hypotheses. In addition, LFA requires the discussion of external factors in the outcomes-to-impact considerations; this helps greatly to put the research in context regarding regulations, market trends, and the fit between results and existing workflows. These assets of LFA are in particular beneficial for researchers transferring their methods into a new domain or transferring them towards application. To use problem and result tree the following steps were followed: for the problem tree (i) the core problem, *low clinical activity of antibody-based therapy for cancer patient*, was defined in the center of the diagram, (ii) the important causes leading to the core problem were recognized and listed at the bottom as the roots of the tree, (iii) the adverse effects caused by the core problem were placed at the top of the diagram as the branches of the tree (Figure 1).

On the contrary, for the result tree, (i) the core problem statement was replaced with positive one that is ideal for us. The statement was shown in the middle of the diagram entitled "*high clinical activity of antibody-based therapy for cancer patients*", (ii) the more important causes that lead us to achieve the positive statement were listed at the bottom of the diagram as the roots of tree, and (iii) the expected impacts of achieving the positive statement were listed at the top of the diagram as its branches (Figure 2).

Design of logical framework matrix (the logframe)

The logical framework matrix was documented through PMBOK (22), Ortengren (35), Lakhoua (24), Parsons (36) and Mike Eaton's (11) guidelines. Briefly, a matrix with four rows and columns was organized. In the lowest row named activities, the overall project activities which should be done in regard to the project, were noted. In three other rows, the project objectives were put in a hierarchy from the lowest to the highest level, including outputs (at least one product for each activity), outcomes (project achievements) and impact (those objectives that are shared with other development partners and national government agencies). In the first column, these objectives were clearly explained (description). In second and third columns, we summarized how the project objectives can be monitored (indicators) and evaluated (assessment), respectively. Finally, in the fourth column, the key external factors which are critical to the project's success, outcome achievements, were estimated (assumptions). To complete a comprehensive logframe matrix, we also addressed the preliminary arrangement and resources (inputs) that must be considered along with designing the project (S–1).

Results

According to Figures 1 and 2, the diagram of problem analysis provides an overview of all known causes and adverse effects of the core problem vis-a-vis the result

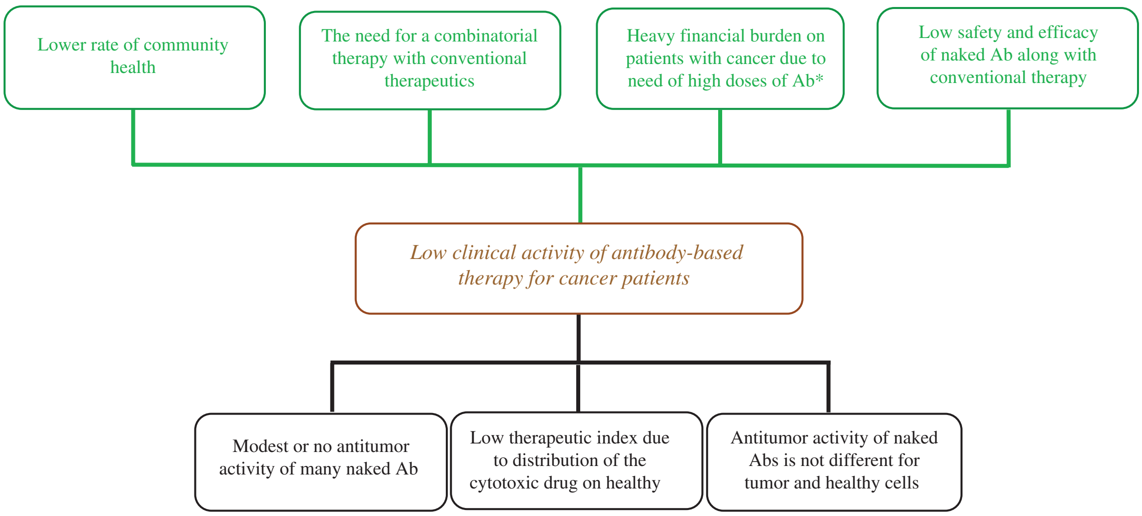

Figure 1: Problem analysis diagram (problem tree), for "low clinical activity of antibody-based therapy for cancer patients"; the three boxes at the bottom of the diagram show the main causes or roots of the problem, the single middle box is dedicated to the core problems itself and becomes the "trunk" of the tree.
The four boxes at the top of the diagram show the consequences (effects) of the core problem which become the branches. *Ab, antibody.

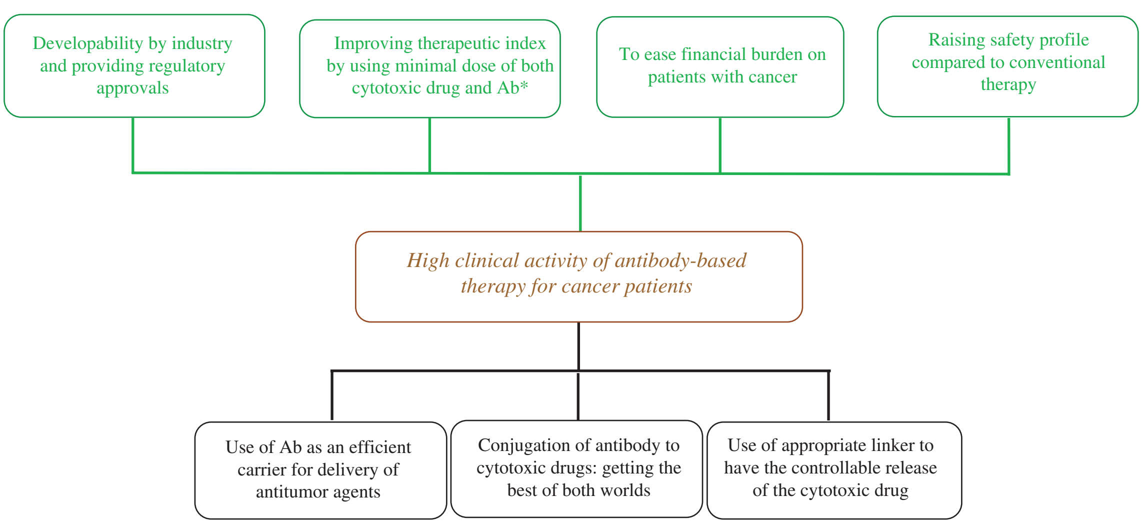

Figure 2: The result tree (also called solution tree), has three parts: a trunk, roots, and branches (effects).
The trunk was created by reversing the core problem statement into positive one as was shown in the center of the diagram. The roots represent the main causes in achieving the statement as written in the center of the diagram (three boxes at the bottom of the diagram) and the branches represent its effects (four boxes at the top of the diagram). *Ab, antibody.

analysis diagram that shows likely causes that may lead to solve the core problem and also the effects that are originated from solving the core problem. Therefore, we used the problem and result tree to chart the reasons that explain why the project, nanomedicine preparation based on ADC, should be undertaken to solve the problem of low clinical activity of antibody-based therapy for cancer patients, (Figures 1 and 2). In other words, it can be used as a document to persuade the sponsors and stakeholders to support the project in order to achieve the main defined goal (positive statement). All indicated project objectives, including outputs, outcomes and impacts, which are usually needed to be answered in proposal templates and instructions, were defined according to the LFA structure. Using the LFA structure in the horizontal dimension, we briefly represented what immediate objects (outputs) need to be delivered from each activity and what project achievements will result in the short-(outcome) and long-(impact) term. In the vertical dimension, we summarized how the progress and ultimate successes of the project will be measured (indicators) and how the information on the indicator will be verified (assessments), also what

Table 1: Logical framework approach matrix (logframe matrix), is a goal oriented project planning tool that can provide a logframe structure for summarizing project requirements to achieve all project deliverables (activities), the project's immediate results which are achieved after doing each activity (outputs), project mid-term results (outcomes), and long-term result (impacts), quantitative and/or qualitative means to measure project results (indicators), how the information on the indicator will be collected (assessments) and what criteria we have assumed to achieve the results (assumptions).

	Description	Indicators	Assessments	Assumptions
Impact	Improving the human health	Enhance efficiencies of healthcare services, cost-savings,…	Existing treatments/quality of life of the patients	The Ministry of Health and industry are interested in adopting new technologies
Outcomes	1. Income from patents and technology transfer	Selling the patent	Financial return documents	Industrial interest towards the project's technology
	2. Translational success	Validate the ADC as an promising drug	Project approval for preclinical development	Only the best drugs go into costly development
Outputs (Deliverables)	1. Characterized antibody	Deliver indicated amount of the characterized antibody	ELISA, flowcytometry, blotting,…	
	2. Linkable cytotoxic agent	Deliver indicated amount of the linkable cytotoxic agent	Mass, IR, and NMR analysis results,…	Selecting team members with skill suitable to undertake the activities
	3. End-point product (ADC)	Deliver indicated amount of the end product (ADC), papers and patent publication	LC-MS, HPLC, DLS, TEM analysis results, amount of papers and patents	
	4. Standing operating procedure (SOP) for managing the disposal of the project's waste and its deliverables side effects	Deliver SOP in a specification data sheet	Through standardized and validated methods Confirmation by healthcare professionals	Nanosafety is one of the main concerns for national/international regulatory agencies
Activities	1. Choosing an appropriate antibody and its targeting characterization on specified cancer cells 2. Synthesis modified cytotoxic agent to link with antibody 3. Antibody drug conjugate (ADC) preparation and formulation 4. Assessment of the environmental, health, and safety challenge regarding project and its outputs			Adequate budget allocations are made The project supporter upholds financial commitment

condition needs to be present for the project to produce the intended activities and results (assumptions) (Table 1). In addition, to have a comprehensive project document, we also provided what preliminary arrangements (Table S-1) and what general inputs/ resources including human, technical, infrastructural, etc. (Table S-2) are necessary to begin the project's activities.

Discussion

We demonstrated that OOPP is a capable and practical methodology to include when considering safety and health concerns during the planning and monitoring of high-tech research projects. In our case study the LFA of a nanomedicine project leads to the inclusion of non-obvious safety requirements like a project activity (Table 1, activity # 4) which consequently results in a main output, standing operating procedure (SOP) for managing the disposal of waste from the project and its deliverable side effects (Table 1, output # 4). According to previous studies regarding nanotoxicity and the translational challenge (1, 3, 12, 14), it is very important to consider the unknown and hidden risks associated with nanomedical innovations.

In this regard, we suggest delivering SOP for managing nanotech research projects waste disposal and their deliverable side effects as an essential output. This output not only can be applied as a useful strategy for eliminating potential human and environmental health hazards of nanostructured molecules, but also provides a competitive edge for projects in achieving their business goals.

Representation of project management tools based on the case studies can permit their wide usage especially for emerging fields of research and their prospects (20, 23, 27). This paper also illustrates a user-friendly template of project management tools for novice project managers who are eager to transfer nanomedicines concepts along the decision points. The template summarizes all of the practical aspects to start a research project in a goal-orientated manner, including:

1. Definition of the scope of the problem and a project that should be undertaken to solve the problem (Figures 1 and 2),
2. Preparation of procurement strategy (supplementary data),
3. Overall action plan (activities as shown in Table 1),
4. Full scope definition that includes output, outcome and impacts (Table 1),
5. Evaluation of project achievement (indicator and assessment columns in Table 1),
6. Risk identification while conducting the project (assumption column in Table 1). Taken together all the practical aspects provide brief project proposal documentation for granting bodies to make the easy and correct decision whether or not to support the project.

Conclusions

Based on our nanomedicine research case study, the effectiveness of OOPP and in particular LFA concerning nanosafety before the translational steps was clearly demonstrated. This provides a systematic approach for managing nanosafety toward translational successes. Although this study was done based on a case study in nanomedicines-research and in particular in the field of tumor-targeted nanomedicines, the translational challenge, nanosafety, described in this paper does not only apply to nanomedicine projects. Therefore, the described OOPP/LFA approach and its necessity to deliver SOP for managing waste disposal from projects and its deliverable side effects, as a main output, can be translated to lessen safety concerns regarding emerging research projects.

Acknowledgments: The project entitled "Nanomedicine preparation based on ADC" is supported by the Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS) (grant no. 92-03-159-25467) in framework of the PhD program. The authors would like to thank Tehran University of Medical Sciences for financial support and declare no conflict of interest in this research work. We also would like to thank Dr. Roya Ghods from the Monoclonal Antibody Research Center (MARC) for her helpful suggestions regarding the original manuscript.

Conflict of interest statement: Authors state no conflict of interest. All authors have read the journal's publication ethics and publication malpractice statement available at the journal's website and hereby confirm that they comply with all its parts applicable to the present scientific work.

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Supplemental Material: The online version of this article (DOI: 10.1515/ejnm-2015-0050) offers supplementary material, available to authorized users.

Bionotes

Mohammad-Reza Nejadmoghaddam
Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS), P.O. Box 14155-6451, Tehran, Iran; and Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran

Mohammad-Reza Nejadmoghaddam received his BSc and MSc degrees in Microbiology from Azad University – Tonekabon (1999) and Jahrom Branches (2006), respectively. Since January 2012, he has been a PhD candidate in Nanomedicine at Nanotechnology Research Center, School of Pharmacy, Tehran university of Medical Sciences (TUMS). His PhD thesis is focused on nanomedicine investigating a new generation of antibody-drug conjugates (ADCs). Nejadmoghaddam's professional life started in 2001 as a microbiologist in the Department of Medical Diagnostics and Biological Products affiliated to ACECR and he was promoted as an academic faculty member to the Nanobiotechnology Research Center at Avicenna Research Institute (ARI), http://www.ari.ir, in 2006. He also trained in project management theory and the management of research projects in his PhD course and currently is working as a manager of central research laboratories of the ARI.

Abdolreza Babamahmoodi
Health Management Research Center, Baqiyatallah University of Medical Science, Tehran, Iran

Abdolreza Babamahmoodi received his MD from Shiraz University of Medical Sciences (2000) and studied Psychiatry at University Putra Malaysia (UPM) (2005) and obtained a PhD in Health Services (research and technology in health systems) from Walden University (2012). He joined Baqiyatallah University of Medical Sciences (BMSU) in Iran as an Assistant Professor in 2013. His research interest includes but is not limited to research in medical sciences, health systems, project management and modeling.

Arash Minai-Tehrani
Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran

Arash Minai-Tehrani is an Assistant Professor at the Avicenna Research Institute, Tehran, IRAN. He received his BS from Azad University in Tehran and his MS and PhD from South Korea. His personal research interests include cancer and gene therapy to find a new method for targeted cancer therapy, risk and reliability, and project management.

Amir-Hassan Zarnani
Nanobiotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran

Amir-Hassan Zarnani is a Professor in Immunology. He earned his doctoral degree in Medical Laboratory Sciences from Shahid Beheshti University of Medical Sciences of Iran (1993) and his PhD from Tarbiat Modares University (2004). His main focus of interest is using the inspiration of reproductive immunology to discover novel modalities for cancer immunotherapy. He is director of Nanobiotechnology Research Center affiliated to Avicenna Research Institute.

Rassoul Dinarvand
Nanotechnology Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS), P.O. Box 14155-6451, Tehran, Iran; and Department of Pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences (TUMS), P.O. Box 14155-6451, Tehran, Iran, Phone: +982164121125, Fax: +982122432021,
dinarvand@tums.ac.ir

Rassoul Dinarvand, received his PharmD from the University of Tehran in 1988. He then successfully completed his MSc in 1990 and his PhD in 1993 in the field of Controlled Drug Delivery Systems at the University of Manchester, UK. He then joined Faculty of Pharmacy, Tehran University of Medical Sciences in 1994 as a faculty member. He was promoted to full professorship in Pharmaceutics in 2005. He was the Dean of the Faculty of Pharmacy at Tehran University of Medical Sciences in 2009 for 4 years. Prof Dinarvand has been active in pharmaceutical administration in both industry and government. He has also been involved in pharmacoeconomy and national drug policy research. However, his main research interest is in the area of polymeric controlled drug delivery systems and he has published over 200 international papers in this field. In recent years he has focused on the design and application of nano-structures as targeted drug delivery systems mainly in the field of cancer treatment. He is the founder and director of the Nanotechnology Research Centre, Tehran University of Medical Sciences. His list of publication can be found at: http://scholar.google.com/citations?user=FF109UoAAAAJ https://www.researchgate.net/profile/Rassoul_Dinarvand/