Assessment sheet technological dimensions of radical innovation

This document's purpose is providing the framework and background of the analysis of the technological dimensions of radical innovation and illustrate it using the example of the SCID-hu-mouse. Herewith, we try to assist in uniformity and consistency of an in-depth validation exercise by different assessors.

1.Defining the technology

In order to assess novelty and impact of a technology, it is necessary to agree upon what exactly defines a technology. Relying on the work of Brian Arthur (2007, 2009) we propose following definition:

> *A technology is defined as a means to fulfill a human purpose. It combines elements/components in a certain way in order to fulfill a purpose, exploiting some natural effect(s) (a truism or phenomenon provided by our surroundings e.g.: gravity, Newton's laws, a certain chemical reaction,…).*

Provided this definition, defining and understanding a technology includes following steps:

1) Identifying the purpose or goal to be served
2) Identifying the components and understanding their interplay in allowing the purpose to be served (understanding and explaining its functionality)

Once these steps are concluded, one can engage in assessing the novelty of the functionality a technology provides.

Illustration based on SCID-hu-mouse:

Background

(Emphasis added)

> Despite advances in the laboratory, the information base *(about the complex interactions within the human body)* remains incomplete and transfer of existing knowledge to the clinic is difficult (McCune et al 1991 p. 400). […] A basic premise underlying previous experiments with the SCID-hu mouse was that an animal model for HIV infection would be most useful if the animal were small, permissive for replication of HIV, and replete with the human cells and organs that represent targets for HIV infection in humans. Of these, the last criterion is perhaps the most important (McCune et al 1991 p. 401). It is one thing to test an antiviral compound against HIV in the laboratory. It is quite another then to move the compound to the clinic and show that it might also work against HIV in humans (McCune et al 1991 p. 420-21).

Purpose of the technology

Providing an environment for investigation of HIV in vivo and clinical testing of potential drugs for HIV in humans which is as close as possible to the real human environment.

Functionality of the technology

For the identification of the components used and their role in serving the purpose, we identify (based on McCune et al 1991) the different sub-problems that were solved by incorporating the components and concepts embodied in the invention.

If a small animal could be complemented with the interactive organs of the human hematopoietic system, two advantages might result: The small animal might then demonstrate long-term multilineage reconstitution with human hematopoietic cells, and the human organs in the animal could serve as targets for infection by HIV. **To create this animal model, it was important (a) first to find an animal that would not reject the human organs and, (b) second, to develop means by which the human cells would not reject the host animal** (McCune et al 1991 p. 402). (*subproblems to be solved for proper functionality*)

Solution to (a) : The first requirement was met with the selection of the C.B- 1 7 scid/scid mouse. This mouse stock, described by Bosma and colleagues in 1983 (Bosma et al, 1983), has a defect in a lineage-restricted progenitor to the T- and B-cell series (McCune et al 1991 p. 402).

Solution to (b) :To reconstitute the SCID mouse with human hematopoietic organs, it was important **that mature human T cells be excluded** (subproblem A). Otherwise, graftversus-host disease might ensue. It was also important to provide a **source of human hematopoietic stem cells**, so that the human system could selfrenew (subproblem B). The use of human fetal liver satisfied both requirements (McCune et al 1991 p. 403) (solution to both subproblems). […]**The animals so constructed have been termed "SCID-hu mice."**

Summary of the technology

In general terms, these are **immunodeficient mice *(SCID-mice)*** that are **surgically engrafted** with **component organs of the human hematopoietic system, including human fetal liver, bone marrow, thymus, lymph node, spleen, skin, and/or gut.** The human organs are accepted; human hematopoiesis proceeds. The human T cells mature within the mouse; graft-versus-host disease does not occur.

2.Assessing novelty in functionality

Since the concept of novelty always implies some 'change' from what previously existed (meaning that every different embodiment of components to serve a goal can be considered as new), it is important to qualify the concept of 'change' and the assessment of 'magnitude of change' in the context of

technological development. (1) What can be considered as the potential attributes on which one technology can differ from another? (2) Given these attributes, how do we define 'more/less different'.

A) *Novelty of components to the purpose at hand*

A1: Given a certain purpose, to what extent does the technology embody different (combinations of) components compared to previous technologies with the same purpose?

> None of its (combination of) components are different (score=1)

> All of its (combinations of) components are different (score=10)

A2: Concerning the new (combinations of) components identified in (1): they were used before to serve purposes related to the purpose of the invention at hand/they were used before, but only to serve purposes unrelated to the purpose at hand/they were never used in any technology before.

> They were used before to serve purposes very similar to the purpose of the invention at hand (score=1)

> They were used before, but only to serve purposes unrelated to the purpose at hand (score=5)

> They were never used in any technology before (score=10).

B) *Novelty of principles of working to the purpose at hand*

B1: Given a certain purpose, to what extent does the technology embody different principles of working (guiding the selection of the combination of components) compared to previous technologies with the same purpose?

> None of its principles of working exploited are different (score=1)

> All of its principles of working exploited are different (score=10)

B2: Concerning the principles of working newly exploited to serve the purpose of the invention at hand identified in (1): they were used before to serve purposes related to the purpose of the invention at hand/they were used before, but only to serve purposes unrelated to the purpose at hand/they were never used in any technology before.

> They were used before to serve purposes related to the purpose of the invention at hand (score =1)

> They were used before, but only to serve purposes unrelated to the purpose at hand (score =5)

> They were never used in any technology before (score =10).

Illustration based on SCID-hu-mouse:

Existing technologies with the same purpose

Up until the invention of the SCID-hu-mouse, investigation of HIV and testing of potential agents for treatment was limited to in vitro studying of the mechanisms that play. (**MORE INFORMATION ON EXISTING METHODS AND THEIR WORKINGS IS NECESSARY**)

A1: Identification of (combinations of) components new to the purpose at hand

-Use of a 'Severe Combined ImmunoDeficient (SCID) mouse' (Bosma et al., 1983)

-Use of component organs of the human hematopoietic system surgically engrafted in the mouse (human fetal liver, bone marrow, thymus, lymph node, spleen, skin, and/or gut)

(-Combination of those components)

Score: **8**

Explanation: The components that are key to how the technology functions have not been used before for this purpose which is why the invention should score high. However, some components can be considered as 'standard practice' (f.e.: use of HIV-infected blood of patients was used before in in vitro methods).

A2: Degree of novelty of components

-First time the SCID-mouse was used for any technological application **(TO BE CHECKED!)**

-First time the component organs (altogether) of the human hematopoietic system were implanted in an animal with a technological purpose in mind. Previously, allogeneic or xenogeneic skin was accepted by SCID-mice, as well as hybridoma cells from different species including humans. **WHAT ABOUT TRANSPLANTING THESE ORGANS IN OTHER ANIMALS (FOR TESTING OF DISEASES)?**

(THIS IS WHAT I ASSUME BASED ON MCCUNE ET AL., 1991, P 403)

-Consequently, the combination was also never used in any technology before

BASED ON INFORMATION GATHERED SO FAR:

Score: **8**

Explanation: The new (combinations of) components were often never used to in application to a purpose. However, some embryonic experiments to applications similar to the one at hand seemed to exist.

B1: Identification of principles of working new to the purpose at hand

-The principle that SCID-mice have a deficiency in their immune system such that it does not attack foreign tissue

-The principle that human fetal liver is important in the early stage of the production of mature human T cells (this meant that the entire process of hematopoiesis proceeds in the body of the mouse)

-The principle that human hematopoiesis proceeds when the component organs are present

Score: **8**

Explanation: The principles that are key to how the technology functions have not been exploited for this purpose before, the invention should score high. However, some principles of working exploited were well-used for this purpose (f.e.: the principle that HIV affects the human organs used in this invention was established).

B2: Degree of novelty of principles of working

-The principles identified in B1 can be considered as existing before, and they were used for purposes that are related to the purpose at hand (MORE REFERENCE MATERIAL NEEDED)

Score: **5**

Explanation: (more reference material needed)

3.Assessing novelty in origins

Although novelty in functionality can be seen as the backbone of the novelty construct regarding technology, it does not explicitly incorporate the sources of knowledge from which the inventors drew to achieve the novel functioning of the technology. Once developers of a technology are convinced of a new approach to serve a purpose, a range of problems/sub-problems are to be translated to requirements solving them. A characteristic of drastic developments in the evolution of technology is that the domains of knowledge used to come to candidate-solutions to these problems change compared to common practice in a field. Novelty in origins is a construct with which we want to capture this 'phenomenon'. We can view novelty in functionality as a result from change in knowledge 'sources' used to address problems in certain domains, while the use of different knowledge sources might, on the other hand, also be a result from problems encountered when trying to make a new technology functional.

To assess novelty in knowledge origins, one would want to identify the problems/sub-problems encountered and solved by the technology at hand. Next, we should look at the domains of knowledge from which inventors drew to solve these problems and assess their novelty to the purpose at hand.

Given a thorough understanding of the functioning of the technology at hand, we map the knowledge necessary to understand why the embodiment of the components is a solution to achieve the purpose at hand (which knowledge is pivotal to have come to the invention). We make a distinction between knowledge previously used in a technology and knowledge stemming from scientific activity. Once identified the knowledge origins, we assess whether this knowledge was previously used for the purpose in the invention. If the answer is negative, we assess the degree of novelty of this new application of knowledge.

→Provide a clear overview of the origins of scientific and technological knowledge used for this invention

A) Novelty of scientific origins

A1: Given its purpose, to what extent are the scientific origins of the technology different compared to the scientific origins of technologies with the same purpose?

    None of the scientific origins are different (score=1)

    All of the scientific origins are different (score =10)

A2: Concerning the new scientific origins identified in A1:

    They were used before to serve purposes related to the purpose of the invention at hand (score =1)

    They were used before, but only to serve purposes unrelated to the purpose at hand (score =5)

    They were never used in any technology before (score =10)

B) Novelty of technological origins

B1: Given its purpose, to what extent are the technological origins of the technology different compared to the scientific origins of technologies with the same purpose?

    None of the technological origins are different (=1)

    All of the technological origins are different (=10)

B2: Concerning the new technological origins identified in (1):

    They were used before to serve purposes related to the purpose of the invention at hand (=1)

    They were used before, but only to serve purposes unrelated to the purpose at hand (=5)

    They were never used in any technology before (=10)

Illustration based on SCID-hu-mouse:

Identification of problem sequence and knowledge origins

We try to sketch the problem-solution sequence leading to the invention at hand and point out the general origins of knowledge used to come to the invention:

Main purpose (problem to be solved): Providing an environment for investigation of HIV in vivo and clinical testing of potential drugs for HIV in humans which is as close as possible to the real human environment.

> *Problem 1:* Although many steps of the life cycle of HIV have been delineated and inhibitors to most have been proposed as therapeutics, little is known about the events that occur immediately after infection with HIV or those that herald the progressive course toward full-blown AIDS. Consequently, it is difficult to decide when to intervene with therapeutic compounds or which ones to use (many possible candidates). None of the proposed components can be tested for efficacy against HIV in vivo, prior to use in humans.

> *KO1 (knowledge origin):* the problem is identified entirely based on knowledge in the field of HIV treatment/testing.

> *Solution 1:* Use a small animal model designed specifically for the study of complex human organ systems in vivo, using human organs to reconstruct the human hematopoietic system.

> *KO2:* The solution of using a small animal model was based on knowledge in the field of HIV.
> *KO3*: Using organs engrafted in animals was based on knowledge … (TO BE CHECKED).

> > *Problem 1.1:* To make the solution proposed to function properly, the small animal should be made sure not to reject the organs envisioned to be engrafted into them.

> > *KO4:* The problem was identified using the knowledge about graft-versus-host-disease which might entail from implanting foreign tissues into organisms.

> > *Solution 1.1:* Use the SCID-mouse

> > *KO5:* The solution provided draws from an experiment ('the Bosma paper': Bosma et al., 1983) which shows that mice with an autosomal recessive mutation suffer from Severe Combined ImmunoDeficiency (SCID). The experiment frames in the genetic human disease SCID and provides a new animal model for it (previously observed in Arabian foals). Furthermore, the identified mice were previously shown to accept grafts of allogeneic or xenogeneic skin with ease, as well as hybridoma cells from humans. Therefore it stood to reason that this animal might accommodate grafts of human hematopoietic organs as well. Finally, knowledge about the susceptibility to PCP (an infection that rarely affects other immunodeficient strains such as nude mice) of the animal made testing of the success of the transfer of the immune system (produced by human hematopoiesis) possible.

Problem 1.2: Human cells should not reject the host animal in order to make the hematopoiesis to proceed in the animal.

> *Sub-problem 1.2.1:* Mature human T-cells should be excluded in order to prevent graft-versus-host-disease.

> *Sub-problem 1.2.2:* A source of human hematopoietic stem cells needed to be provided to ensure hematopoiesis to proceed in the animal.

Solution 1.2: Use human fetal liver, as well as other organs active in the hematopoietic process.

KO6: Page 402/403 describes how 'hematopoiesis occurs as a result of self-renewal, proliferation, and/or differentiation of cells in a dynamic flow within and between organs'. This knowledge provides the input of the identification of sub-problems 1.2.1 and 1.2.2 and was knowledge drawn from when deciding to use fetal liver in combination with other human organs that provided the solution.

KO7: Specifically, knowledge about the facts that human fetal liver is free of mature $C3^+$ human T cells and also contains human hematopoietic progenitor cells was drawn from to come to solution 1.2

Novelty of knowledge origins

> ***A.*** *Novelty of scientific origins*

A1. *Score: 7*

Explanation: KO4, KO5, and KO7 where knowledge origins embedded in scientific fields from which technologies with the same purpose have not drawn from.

A2. *Score: 5*

Explanation: The purpose of the technologies usually drawing from these fields have purposes that can be seen as related to the purpose of this invention.

> ***B.*** *Novelty of technological origins*

W<small>E NEED MORE REFERENCES CONCERNING</small> KO'<small>S TO ASSESS WHETHER THEY MIGHT HAVE BEEN EMBEDDED IN</small> <small>TECHNOLOGIES AND WHETHER THE CURRENT INVENTION MIGHT DRAW FROM KNOWLEDGE IN PREVIOUS</small> <small>TECHNOLOGIES.</small>

4.Assessing technological impact

A third construct we introduce to characterize radicalness of an invention is its technological impact. A first sub-dimension we introduce is technological performance. The reason we treat this as part of the impact (and as such an ex post measure) is that the performance increase might only become assessable after some time has passed. We assess performance increase by comparing the success with which the purpose of the technology is served with the success of the state-of-the-art performance before the new technology arrived. If no well-defined performance feature can be given, it is important to define performance on the relevant attributes mentioned in the literature.

A) *Performance increase*

> To what extent was the goal set out to be served by the invention accomplished better compared to state-of-the-art practices at the moment of the invention?
>
> It had no overall performance increase (=1)
>
> It made possible significant improvements compared to current practice, but still a number of significant problems are not assessed (=5)
>
> It represented a major leap in performance and the goal set out is served completely thanks to the invention (=10).

Regardless of direct performance increase of an invention, impact of an invention might be reflected by technological accumulation (i.e. further technological developments due to the focal technology). We make two distinctions when assessing technological accumulation:

First, we distinguish between direct and indirect effects on the course of future technological developments. With direct effects we mean the effect a technology as a whole has on future technologies. An invention (for instance a piezo-electric element) might be used as a component in future technological developments (more efficient car engines). With indirect effects we mean the effect an invention might have by re-use of some concept or component contained in it by further technologies. An invention (for instance the first embodiment of the jet engine) might have a principle of working (jet propulsion) which is used by follow-up technologies (turbo-jet engine).

Second, we distinguish between broad and narrow accumulation of technology. This distinction pertains to the number of purposes to which a technology has an impact.

Finally, we assess whether the technology has impact on technological fields which were hitherto not drawing from technologies from the technological field of the focal technology.

B) *Technological accumulation*

B1) *Broadness of impact*

> **B1a:** To what extent did the technology have an impact on technologies that serve purposes different to the technology at hand?

B1b: Concerning the technologies on which impact was identified above: they serve purposes related to the purpose of the invention at hand/they serve purposes entirely unrelated to the purpose at hand.

They serve purposes very much related to the purpose of the invention at hand (=1)

They serve purposes entirely unrelated to the purpose at hand (=10)

B2) *Magnitude of direct/indirect impact*

B2a: Given the scope of the impact, to what extent was it directly used by a multitude of inventions in the future?

B2b: Given the scope of the impact, to what extent were its (combination of) components used indirectly by a multitude of inventions in the future?

B3) *Novelty of impact*

B3a: To what extent did the technology have impact on technologies that have never before built on the technologies with the purpose of the focal invention?

B3b: Considering the novel impact identified above, to what extent did it pertain to technologies serving purposes unrelated to the purpose of the technology at hand?

A third sub-dimension assesses the extent to which previous technologies are made obsolete by the technology at hand. This might occur either through its direct or indirect impact on future technologies.

C) *Obsoleting previous technologies*

-To what extent were the technologies previously used to serve the purpose of the invention made obsolete by the invention at hand?

No previous technology was made obsolete (=1)

All previous technology were made obsolete (=10)

Illustration based on SCID-hu-mouse:

A) *Performance increase*

The SCID-hu-mouse fulfills the purpose of providing a model for investigating HIV and testing agents against it in a considerably improved way compared to common practice (mainly in vitro methods).

(Summary from page 426 in McCune et al., 1991) Experiments show that human hematolymphoid organs (including fetal liver, bone marrow, thymus, lymph node, skin and mucosal tissue) can be reproducibly engrafted into the SCID mouse after which human hematopoietic progenitor cells move

into and differentiate through the thymus microenvironment. Furthermore, the human lymphocytes of the SCID-hu mouse are phenotypically and functionally normal. Primary and secondary humoral immune responses can be observed. Primary isolates of HIV directly taken from patients will infect the human organs of the mouse (however, lab-adapted isolates do not). The efficacy of AZT (existing anti-HIV drug) is reliably demonstrated, which leads to the conclusion that novel antiviral compounds can now be tested using AZT as a standard.

> *Score:* **7**

> *Explanation:* It considerably improved on performance with regard to the goal, but some problems were not solved yet (see McCune, 1996). He reports on later improvements on the SCID-hu constructs which appear to fulfill the basic parameters of a useful model: SCID-hu thy/liv and SCID-hu Bone models.

B) *Broadness of impact*

The present invention has had impact on technologies with different purposes to the one at hand. These include using the mouse model for the evaluation of viral infectious diseases other than HIV (purpose considered as moderately close to the purpose at hand) and study of human hematopoietic processes (purposes which can be considered as only approximately related).

(McCune 1996) The SCID-hu Bone and Thy/Liv implants appear to reproduce the expected physiology of their human counterparts. Accordingly, they have been applied to the evaluation of biological events that are otherwise difficult to observe. These applications have, to date, been focused primarily in the areas of hematopoiesis and viral infectious diseases:

-   Evaluation of normal human hematopoiesis

-   Identification and characterization of human hematopoietic progenitor cells

-   Evaluation of endogenous and exogenous factors which influence hematopoietic differentiation (e.g., Cytokine interactions, Irradiation, Human stem cell gene therapy, Leukemogenesis, Positive and negative selection in the thymus)

-   Evaluation of viral infectious diseases

-   Evaluation of pathogenic mechanisms of HIV in vivo (e.g., Molecular determinants of pathogenicity in vivo, Thymocyte depletion, Indirect induction of cell death, Infection of intrathymic T progenitor cells

-   Evaluation of therapeutic modalities for HIV infection in vivo

-   Evaluation of other viral infectious diseases in vivo

B1a:

> *Score:* **5**

> *Explanation:* Considerable impact on development of technologies with different purposes (see above), but it cannot be said an extreme number of technologies with different purposes built on it.

B1b:

> *Score:* **5**

> *Explanation:* A number of the technologies it impacted on can be said to be different in purpose, some of which are fairly related (other infectious diseases can be seen as fairly close to HIV) while others are rather minimally related (evaluation of factors influencing hematopoietic differentiation can be seen as rather distant, although still related to the immune system). This brings us to a score of 5.

B2. Magnitude of impact

Direct: -??? Testing of anti-HIV drugs ???

Indirect: McCune (1996) reports a number of refinements to the mouse model. Of these, SCID-hu Bone and SCID-hu Thy/Liv appeared to reproduce the expected physiology of their human counterparts, which led to a number of applications in the areas of hematopoiesis and viral infectious diseases (see above).

B2a *Direct impact*

Score: **3**

B2b *Indirect impact*

Score: **8**

Explanation B2a/B2b: (see also above) we assess the magnitude of direct impact as moderate and the magnitude of indirect impact as large.

B3. Novelty of impact

THE ORIGINS OF THE TECHNOLOGIES IDENTIFIED IN B HAVE TO BE LOOKED UP TO ASSESS WHETHER THIS TECHNOLOGY HAD NEW IMPACT!

C) Making obsolete previous technologies

Score: **3**

Explanation: Although for a number of applications the invention is the preferred way to serve the purpose, it has not made obsolete previous technologies (mainly in vitro methods) obsolete. **MORE REFERENCES NEEDED**

Novelty in Functionality	Novelty in Knowledge Origins	Technological Impact
A. Novelty of components **A1**. Given a certain purpose, to what extent does the technology embody different (combinations of) components compared to previous technologies with the same purpose? None of its (combination of) components are different **(=1)** All of its (combinations of) components are different **(=10)** **8**	**A. Novelty of scientific origins** **A1.** Given its purpose, to what extent are the scientific origins of the technology different compared to the scientific origins of technologies with the same purpose? None of the scientific origins are different **(=1)** All of the scientific origins are different **(=10)** **7**	**A. Performance increase** To what extent was the goal set out to be served by the invention accomplished better compared to state-of-the-art practices at the moment of the invention? It had no overall performance increase **(=1)** It made possible significant improvements compared to current practice, but still a number of significant problems are not assessed **(=5)** It represented a major leap in performance and the goal set out is served completely thanks to the invention **(=10)**. **7**
A2. Concerning the new (combinations of) components identified in A1: They were used before to serve purposes related to the purpose of the invention at hand **(=1)** They were used before, but only to serve purposes unrelated to the purpose at hand **(=5)** They were never used in any technology before **(=10)**. **8**	**A2.** Concerning the new scientific origins identified in A1: They were used before to serve purposes related to the purpose of the invention at hand **(=1)** They were used before, but only to serve purposes unrelated to the purpose at hand **(=5)** They were never used in any technology before **(=10)**. **5**	**B. Technological accumulation** **B1. Broadness of impact** **B1a**. To what extent did the technology have an impact on technologies that serve purposes different to the technology at hand? **5** **B1b.** Concerning the technologies on which impact was identified in B1a: They serve purposes very much related to the purpose of the invention at hand **(=1)** They serve purposes entirely unrelated to the purpose at hand **(=10)** **5**
B. Novelty in natural effects exploited **B1.** Given a certain purpose, to what extent does the technology embody different natural effects (guiding the selection of the combination of components) compared to previous technologies with the same purpose? None of its natural effects exploited are different **(=1)** All of its natural effects exploited are different **(=10)** **8**	**B. Novelty of technological origins** **B1**. Given its purpose, to what extent are the technological origins of the technology different compared to the scientific origins of technologies with the same purpose? None of the technological origins are different **(=1)** All of the technological origins are different **(=10)** **?**	**B2. Magnitude of direct/indirect impact** **B2a**. Given the scope of the impact, to what extent was it directly used by a multitude of inventions in the future? **3** **B2b.** Given the scope of the impact, to what extent were its (combination of) components used indirectly by a multitude of inventions in the future? **8**

		B3) *Novelty of impact*
		B3a: To what extent did the technology have impact on technologies that have never before built on the technologies with the purpose of the focal invention?
		?
		B3b: Considering the novel impact identified above, to what extent did it pertain to technologies serving purposes unrelated to the purpose of the technology at hand?
		?
B2. Concerning the natural effects newly exploited to serve the purpose of the invention at hand identified in (B1): They were used before to serve purposes related to the purpose of the invention at hand **(=1)** They were used before, but only to serve purposes unrelated to the purpose at hand **(=5)** They were never used in any technology before **(=10).** **5**	**B2.** Concerning the new technological origins identified in (B1): They were used before to serve purposes related to the purpose of the invention at hand **(=1)** They were used before, but only to serve purposes unrelated to the purpose at hand **(=5)** They were never used in any technology before **(=10).** **?**	**C. Obsoleting previous technologies** To what extent were the technologies previously used to serve the purpose of the invention made obsolete by the invention at hand? No previous technology was made obsolete **(=1)** All previous technology were made obsolete **(=10)** **3**