Envisioned Developments in Nanobiotechnology

Expert Survey

Summary of Results

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This report is dedicated to the memory of Prof. Aric Menon*, a colleague and a friend.
His professional legacy and personal friendship will always inspire us.

*Aric Kumaran Menon passed away in December 2005 in the age of 49. He was a Professor at MIC – Department of Micro and Nanotechnology, Danish Technical University, and a member of the Foresight and Strategy group in “Nano-to-Life”.

1. Introduction

We present an overview of results of a worldwide expert survey conducted within the Foresight and Strategy workpackage (WP5) of the EU network of excellence "Nano-to-Life" (N2L). Main goal of the survey was to provide a useful perspective on future developments in Nanobiotechnology (NBT) and to contribute to a shared vision regarding the future of NBT research, taking into consideration barriers, ethics and public acceptance, commercialization prospects and the state of basic and applied research.
Specific objectives were:

(1) to prioritise the various developments based on their impacts on science & technology and important socio-economic achievements
(2) to assess the commercialisation prospects of the various technologies and to identify the most promising ones
(3) to identify the necessary measures to foster the realisation of the envisioned developments
(4) to identify consensus, or disagreement, on issues relevant to the long-range development of NBT.

The survey covers 20 foreseen technological and scientific developments in NBT, based on a state of the art (SoA) review prepared during 2004, covering wide range of achievements in NBT. The preparation of the survey involved meetings and discussions with members of WP5 board, N2L Executive Board (ExBo) and scientists from the network. The survey was open to participants within and outside the network - from the scientific community, industry and other sectors. It followed pilot surveys within N2L, in order to make it as relevant as possible to N2L objectives. The survey results will help validate trends that emerged from the SoA review and provide inputs to the NBT roadmapping which will lead to a long-range strategy of research within N2L and beyond (e.g. the envisioned ENBI – the European Nanobiotechnology Institute).
This overview report may be followed by a more detailed report presenting all results available on the different 20 topics one by one.

It is important to note that foresight expert surveys such as the one presented here reflect *professional estimates and judgments* of the participating experts, and not *expectations or wishes*. Expert surveys are an important and widely used tool in foresight. In many foresight studies the surveys are performed in 2-3 rounds (so-called "Delphi survey"), especially when the first round reveals significant disagreements among the experts. In each subsequent run the experts can re-assess their judgments based on the results of the previous run. In this way an iterative (anonymous) group interaction is achieved among the experts, usually converging to a reasonable consensus. Such surveys are considered as a valuable tool used by industrial companies as well as governmental departments and other organizations, in order to elicit the knowledge and bring together the judgments of a *large number* of experts. The expert judgments enable useful analyses and priority-setting, and stimulate further discussions on the future-oriented issues.

2. Scope and content

The online (web-based) survey consisted of 20 statements on future developments in NBT, with a time horizon of ~25 years. The statements were selected based on the N2L State of the Art report and on consultation with WP5 partners as well as other scientists. Of course it was impossible to explore all the envisioned developments and applications of NBT. An inevitable compromise had to be made between the desire to cover as much diverse topics as possible, and the necessity to refrain from a too complex and time-consuming questionnaire.

The first draft of the questionnaire was formulated in the end of December 2004, and a pilot survey was conducted (among WP5 and ExBo members and a few other scientists) in January – February 2005. Corrections were made based on comments from the participants, including some comments obtained after the N2L annual meeting in Munster in March 2005. Finally the WP5 board approved 20 statements representing reasonably wide range of NBT research areas with envisioned applications. Attention was paid to cover the "nano to bio" domain (13 statements) as well as the "bio to nano" domain (7 statements) – see Table 1. A web-based questionnaire was designed and tested in March 2005 and the online survey was conducted in the period from mid April till the end of July 2005. The entire questionnaire required over an hour, however most respondents chose to fill-in only part of the 20 statements.
For each statement the respondents were asked to assess:

- The likely time of realization (*before 2010, 2011-2015, 2016-2020, after 2020, never*)
- The level of impact (*very high, high, low, negative*) on each of the following domains: science & technology, environment, life quality, the labor market
- The commercialization prospects (*very high, high, low*, *impossible*) in the following areas: health & medicine, security, environment, agro-food, consumer products
- What limits the prospects of commercialization (*no needs, needs already fulfilled by other technologies, many barriers, or – no limits at all*) in each of the above-mentioned areas
- What actions are needed to enhance the likelihood of realization (*increase in basic research, increase in applied research, financial measures, regulations, solution of ethical problems, promoting public acceptance*)

Table 1: the survey statements

Statement	Nano to Bio	Bio to Nano
1. **Cellular cycle** Thanks to advances in nanobiotechnology, the fundamental processes of the cellular cycle are mostly understood	x	
2. **In vitro construction of human organs** Advancements in nanobiotechnology enable the construction in vitro of artificial human organs.	x	
3. Nanostructured biomaterials Novel nanostructured biomaterials replace existing materials (e.g. polymers).		X
4. Targeted drug delivery Targeted drug delivery based on nanoparticles becomes a standard tool (for therapeutic purposes, performance enhancement etc).	x	
5. **Smart probes used in in-vivo** Smart probes (that illuminate when reaching their target) are practically used in diagnosis in-vivo.	x	
6. **Biodetection with smart nano-surfaces** Smart and adaptable surfaces at the nanoscale are the basic building block for Biodetection.	x	
7. **Nanotools for manipulation inside cells** Nanotools (e.g. optical tweezers) are used for manipulation inside cells while keeping the cells' integrity and activity.	x	
8. **Nano-agents for analysis inside cells**	x	

Nanosized imaging agents (e.g. quantum dots) are used for analysis and diagnosis inside cells without affecting their normal functionality.		
9. **Bio energy conversion in micro/nano systems** Biological energy conversion systems (e.g. biomolecular motors) are practically used in artificial micro/nano systems.		x
10. **Bio-inspired materials** Advanced bioengineered materials based on bio-inspiration/bio-mimicry are widely used.		x
11. Labs on chip Labs on chip are widely used for various applications, in different sectors, including households.	x	
12. **Protein & DNA chips integrated** Protein chips are integrated with DNA chips for specific diagnosis purposes in current hospital practices.	x	
13. **Protein chips for personal use** Protein chips are widely used by the public for personal use.	x	
14. **Cells on chips replace animal testing** In vitro tests based on cells on chips replace animal testing for various applications (e.g. pharma, cosmetics..).	x	
15. **Biosensors for single molecules** Biosensors for detection of single molecules based on nano arrays (e.g arrays of nanotubes) are commercially available.	x	
16. Self-assembly is widely implemented Self-assembly is widely implemented as a technique for development of materials and devices.		x
17. **Self-repairing in artificial systems** Living self-repairing abilities are implemented in artificial systems.		x
18. **Nanomachines inside the body** Nano-machines for theranostics (therapy and diagnosis) are practically used inside the body.	x	
19. **Chips employing biomolecules** Chips employing biomolecules as active elements are commercially manufactured.		x
20. **Chips made by using DNA / peptides** Nanoelectronics chips are commercially manufactured by using DNA or peptides (as templates or for nanopatterning).		X

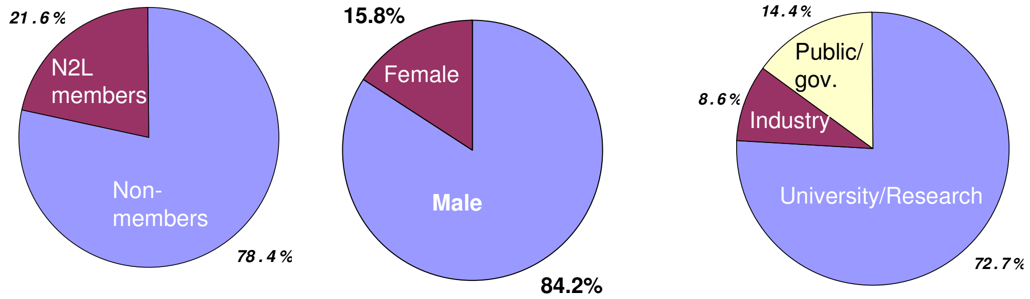
In the next sections we will usually refer to the short titles of the 20 statements. However, when reading the results it is very important to remember the full meaning of each statement. For example, "targeted drug delivery" in this survey means (see Table 1): *"Targeted drug delivery based on nanoparticles becomes a standard tool (for therapeutic purposes, performance enhancement etc)".*

3. General data and respondents' profile

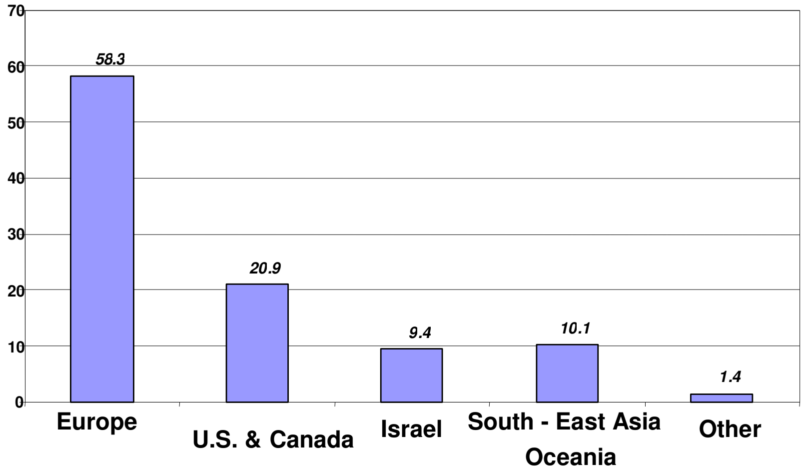
The N2L expert survey was conducted online in the period from 17.4.2005 till 1.8.2005*. (The survey format is shown in Appendix 1).
Over 720 email invitations were sent to potential participants worldwide, identified from the following target groups: N2L members, authors/editors of NBT publications, scientists in NBT research centers and labs, managers of NBT-related industrial firms, etc.
Participation in the survey required registration in the survey website before viewing the questionnaire. 258 people registered, and **139** actually answered at least part of the questionnaire.

* The internal N2L website as well as a special TAU website were used for this purpose. Some responses were obtained on paper.

The number of responds per statement varied from **22** to **79**, with an average of 45. The actual (139) respondents come from 30 countries. The highest numbers of respondents are from USA (27), Germany (18), Israel (13), France (13) and Switzerland (7) – see Table 2. Unfortunately, only 30 respondents are N2L members. Most respondents are males and belong to academic research institutes.



Graph 1: Respondents by N2L membership, gender and affiliation



Graph 2: Distribution of respondents by geographic regions

Table 2: Respondents by country

Country	Number of respondents
1. U.S.A	27
2. Germany	18
3. Israel	13
4. France	13
5. Switzerland	7
6. Italy	6
7. U.K	6
8. Romania	5
9. Spain	5
10. Greece	4
11. Australia	4
12. Austria	3
13. Sweden	3
14. Ireland	3
15. China	3
16. Netherlands	2
17. Canada	2
18. Japan	2
19. Singapore	2
20. Finland	1
21. Denmark	1
22. Norway	1
23. Lithuania	1
24. Belgium	1
25. Bulgaria	1
26. New Zealand	1
27. India	1
28. South Korea	1
29. Nigeria	1
30. Brazil	1
Total	**139**

Because of the diversity of NBT research areas, it is clear that a person can be a specialist in some areas while possessing only limited knowledge in other areas. Therefore, the respondents were asked to state their level of knowledge for each individual statement, according to four categories: “expert”, “knowledgeable”, “familiar” and “unfamiliar”. They were requested not to respond to statements for which they considered themselves as “unfamiliar”. The distribution of respondents by their level of expertise in each statement is shown in Table 3.

In the following results, in some cases the answers of those respondents who qualified themselves as “experts” or “knowledgeable” are highlighted.

Table 3: Respondents' level of knowledge
(N=total number of respondents per statement)

Statement	N	Expert	Knowledgeable	Familiar
1. cellular cycle	79	12.7% (10)	45.6% (36)	41.8% (33)
2. in vitro construction of human organs.	52	3.8% (2)	46.2% (24)	50% (26)
3. nanostructured biomaterials.	68	25% (17)	47.1% (32)	27.9% (19)
4.Targeted drug delivery	73	16.4% (12)	50.7% (37)	32.9% (24)
5. Smart probes used in in-vivo.	41	22% (9)	31.7% (13)	46.3% (19)
6. Biodetection with smart nano-surfaces	53	20.8% (11)	52.8% (28)	26.4% (14)
7.Nanotools for manipulation inside cells	40	20% (8)	30% (12)	50% (20)
8. Nano-agents for analysis inside cells	51	19.6% (10)	39.2% (20)	41.2% (21)
9. Bio energy conversion in micro/nano systems.	33	15.2% (5)	39.4% (13)	45.5% (15)
10. Bio-inspired materials	36	22.2% (8)	33.3% (12)	44.4% (16)
11. Labs on chip	49	22.4% (18)	40.8% (20)	36.7% (18)
12. Protein & DNA chips integrated	31	35.5% (11)	45.2% (14)	19.4% (6)
13. Protein chips for personal use.	31	35.5% (11)	35.5% (11)	29% (9)
14. cells on chips replace animal testing	32	18.8% (6)	43.8% (14)	37.5% (12)
15. Biosensors for single molecules	42	26.2% (11)	47.6% (20)	26.2% (11)
16. Self-assembly widely implemented	47	36.2% (17)	44.7% (21)	19.1% (9)
17. Self-repairing in artificial systems.	22	18.2% (4)	27.3% (6)	54.5% (12)
18. Nanomachines inside the body.	35	25.7% (9)	28.6% (10)	45.7% (16)
19. Chips employing biomolecules	40	22.5% (9)	30% (12)	47.5% (19)
20. Chips made by using DNA / peptides	35	20% (7)	34.3% (12)	45.7% (16)

4. Likely time of realization

In the following table & graph an overview of the likely time of realization for all statements is presented, with distinction between the opinions of all respondents and those self-rated as "experts" or "knowledgeable". The number of respondents (N) from both categories is given for each statement.
Shown are the median value, "25% quartile year" (25% of the respondents think that the statement will realize before this year) and "75% quartile year" (75% think that it will realize before this year[*]).

The time-span between the 25% quartile and 75% quartile indicates the degree of consensus (or disagreement) among the respondents: shorter span means higher degree of consensus.

Also shown is the percentage of respondents who think that the statement under consideration will ***never*** be realized. The "never" answers were excluded in the calculation of the median and the quartiles (they can't be logically integrated), therefore it is important to display them separately.
(Of course, high percentage of "never" in a certain statement indicates disagreement even if the inter-quartile span is short.)

[*] 25% of the respondents think that the statement will realize *after* this year.

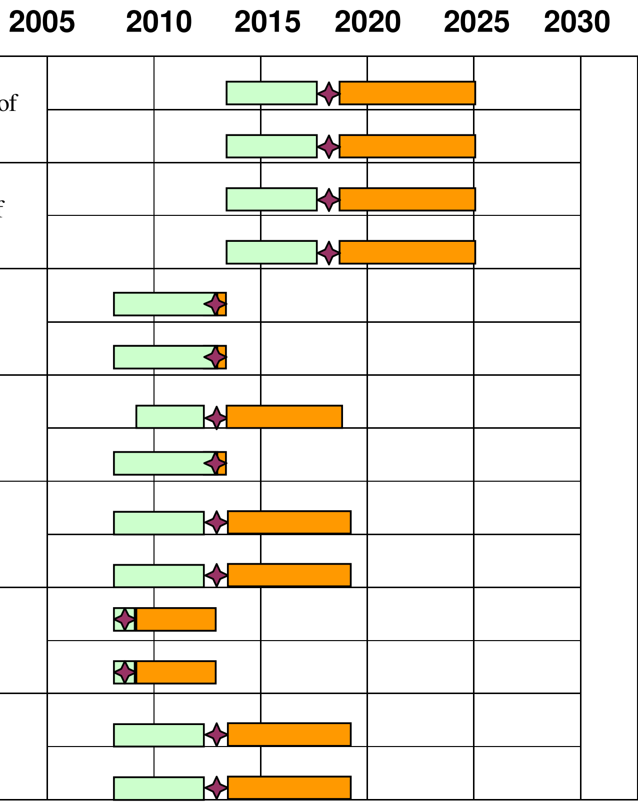
Table 4: Time of realization – all statements

	All Respondents					Experts and Knowledgeable				
Statement	**N**	**25% quartile**	**50% Median**	**75% quartile**	**% Never**	**N**	**25% quartile**	**50% Median**	**75% quartile**	**% Never**
1. cellular cycle	79	2013	2018	2025	7.6	46	2013	2018	2025	6.5
2. in vitro construction of human organs.	51	2013	2018	2025	7.8	25	2013	2018	2025	8.0
3. nanostructured biomaterials.	64	2008	2013	2013	10.9	46	2008	2013	2013	13.0
4.Targeted drug delivery	73	2009	2013	2018	1.4	49	2008	2013	2013	2.0
5. Smart probes used in in-vivo.	40	2008	2013	2018	5.0	22	2008	2013	2018	0
6. Biodetection with smart nano-surfaces	52	2008	2008	2013	0	38	2008	2008	2013	0
7.Nanotools for manipulation inside cells	39	2008	2013	2018	12.8	19	2008	2013	2018	5.3
8. Nano-agents for analysis inside cells	51	2008	2008	2013	5.9	30	2008	2008	2018	0
9. Bio energy conversion in micro/nano systems.	33	2013	2018	2025	12.1	18	2013	2021	2025	11.1
10. Bio-inspired materials	36	2008	2013	2018	0	20	2008	2013	2013	0
11. Labs on chip	46	2008	2013	2018	0	31	2008	2013	2013	0
12. Protein & DNA chips integrated	31	2008	2013	2014	0	24	2008	2013	2016	0
13. Protein chips for personal use.	31	2013	2018	2018	25.8	22	2013	2015	2018	18.2
14. cells on chips replace animal testing	32	2012	2013	2018	18.8	20	2008	2013	2013	20.0
15. Biosensors for single molecules	42	2008	2013	2018	4.8	31	2008	2013	2015	6.5
16. Self-assembly widely implemented	47	2008	2013	2015	4.3	38	2008	2013	2014	0
17. Self-repairing in artificial systems.	22	2013	2018	2025	22.7	10	2013	2015	2025	20.0
18. Nanomachines inside the body.	35	2018	2025	2025	11.4	19	2013	2021	2025	15.8
19. Chips employing biomolecules	39	2008	2013	2018	5.1	20	2008	2013	2013	5.0
20. Chips made by using DNA / peptides	34	2013	2013	2025	5.9	19	2013	2013	2025	0

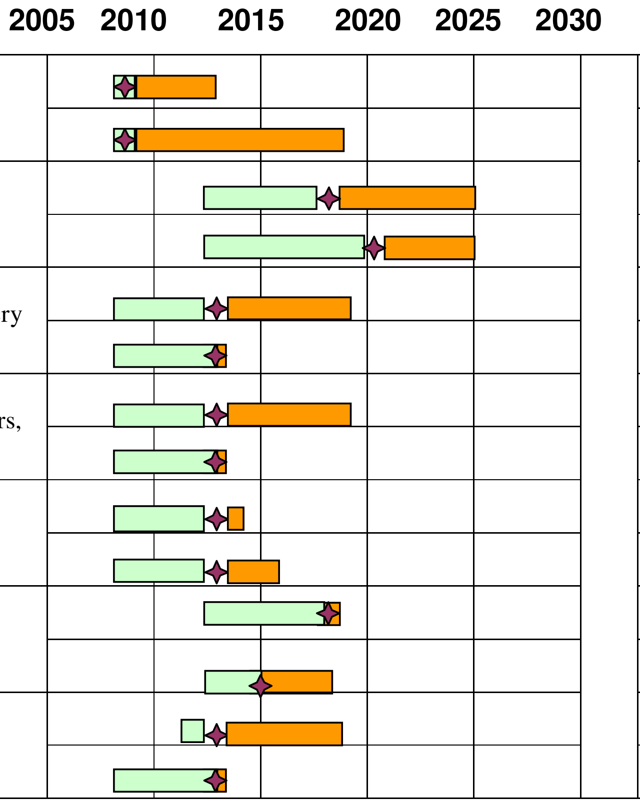
Graph 3: Time of realization – all statements

25% quartile   Median   75% quartile

1[st] line in each statement: all respondents
2[nd] line: experts/ & knowledgeable



Statement	N	"Never"
1. Cellular cycle Thanks to advances in nanobiotechnology, the fundamental processes of the cellular cycle are mostly understood	79	7.6 %
	46	6.5%
2. In vitro construction of human organs Advancements in nanobiotechnology enable the construction in vitro of artificial human organs.	51	7.8%
	25	8.0%
3. Nanostructured biomaterials Novel nanostructured biomaterials replace existing materials (e.g. polymers).	64	10.9%
	46	13%
4. Targeted drug delivery Targeted drug delivery based on nanoparticles becomes a standard tool (for therapeutic purposes, performance enhancement etc).	73	1.4%
	49	2.0%
5. Smart probes used in in-vivo Smart probes (that illuminate when reaching their target) are practically used in diagnosis in-vivo.	40	5.0%
	22	0%
6. Biodetection with smart nano-surfaces Smart and adaptable surfaces at the nanoscale are the basic building block for Biodetection.	52	0%
	38	0%
7. Nanotools for manipulation inside cells Nanotools (e.g. optical tweezers) are used for manipulation inside cells while keeping the cells' integrity and activity.	39	12.8%
	19	5.3%



	N	"Never"
8. Nano-agents for analysis inside cells Nanosized imaging agents (e.g. quantum dots) are used for analysis and diagnosis inside cells without affecting their normal functionality.	51	5.9%
	30	0%
9. Bio energy conversion in micro/nano systems Biological energy conversion systems (e.g. biomolecular motors) are practically used in artificial micro and nano systems.	33	12.1%
	18	11.1%
10. Bio-inspired materials Advanced bio-engineered materials based on bio-inspiration/ bio-mimicry are widely used.	36	0%
	20	0%
11. Labs on chip Labs on chip are widely used for various applications, in different sectors, including households.	46	0%
	31	0%
12. Protein & DNA chips integrated Protein chips are integrated with DNA chips for specific diagnosis purposes in current hospital practices.	31	0%
	24	0%
13. Protein chips for personal use Protein chips are widely used by the public for personal use.	31	25.8%
	22	18.2%
14. Cells on chips replace animal testing In vitro tests based on cells on chips replace animal testing for various applications (e.g. pharma, cosmetics…).	32	18.8%
	20	20%

	2005	2010	2015	2020	2025	2030	N	"Never"
15. Biosensors for single molecules Biosensors for detection of single molecules based on nano arrays (for example, arrays of nanotubes) are commercially available.							42	4.8%
							31	6.5%
16. Self-assembly widely implemented Self-assembly is widely implemented as a technique for development of materials and devices.							47	4.3%
							38	0%
17. Self-repairing in artificial systems Living self-repairing abilities are implemented in artificial systems.							22	22.7%
							10	20.0%
18. Nanomachines inside the body Nano-machines for theranostics (therapy and diagnosis) are practically used inside the body.							35	11.4%
							19	15.8
19. Chips employing biomolecules Chips employing biomolecules as active elements are commercially manufactured.							39	5.1%
							20	5.0%
20. Chips made by using DNA / peptides Nanoelectronics chips are commercially manufactured by using DNA or peptides (as templates or for nanopatterning).							34	5.9%
							19	0%

Based on the above results, the statements can be grouped by their likely time-frames of realisation:

Short term – before 2010:

6. Smart and adaptable surfaces at the nanoscale are the basic building block for Biodetection.
8. Nanosized imaging agents (e.g. quantum dots) are used for analysis and diagnosis inside cells without affecting their normal functionality.

Medium term –2011- 2015:

3. Novel nanostructured biomaterials replace existing materials (e.g. polymers).
4. Targeted drug delivery based on nanoparticles becomes a standard tool (for therapeutic purposes, performance enhancement etc).
5. Smart probes (that illuminate when reaching their target) are practically used in diagnosis in-vivo.
7. Nanotools (e.g. optical tweezers) are used for manipulation inside cells while keeping the cells' integrity and activity
10. Advanced bioengineered materials based on bio-inspiration/bio-mimicry are widely used.
11. Labs on chip are widely used for various applications, in different sectors, including households.
12. Protein chips are integrated with DNA chips for specific diagnosis purposes in current hospital practices.
14. In vitro tests based on cells on chips replace animal testing for various applications (e.g. pharma, cosmetics..).
15. Biosensors for detection of single molecules based on nano arrays (e.g arrays of nanotubes) are commercially available.
16. Self-assembly is widely implemented as a technique for development of materials and devices.
19. Chips employing biomolecules as active elements are commercially manufactured.
20. Nanoelectronics chips are commercially manufactured by using DNA or peptides (as templates or for nanopatterning).

Long term –2016- 2020:

1. Thanks to advances in nanobiotechnology, the fundamental processes of the cellular cycle are mostly understood
2. Advancements in nanobiotechnology enable the construction in vitro of artificial human organs.
9. Biological energy conversion systems (e.g. biomolecular motors) are practically used in artificial micro/nano systems
13. Protein chips are widely used by the public for personal use
17. Living self-repairing abilities are implemented in artificial systems

Very long term ~2025:

18. Nano-machines for theranostics (therapy and diagnosis) are practically used inside the body.

Degree of consensus on the time of realization

The degree of consensus on the time of realization differs considerably among the statements.

Statements with the ***highest*** degree of agreement (interquartile span 5 years) are:
3. Nanostructured biomaterials.
6. Biodetection with smart nano-surfaces
8. Nano-agents for analysis inside cells

Statements with the ***lowest*** degree of agreement (interquartile span 12 years) are:
1. cellular cycle (43% before 2015, 30% after 2020)
2. in vitro construction of human organs (37% before 2015, 31% after 2020)
9. Bio energy conversion in micro/nano systems (36% before 2015, 33% after 2020)
17. Self-repairing in artificial systems (32% before 2015, 23% after 2020)
20. Chips made by using DNA / peptides (50% before 2015, 35% after 2020)

Statements with high percentage of "never":
It is important to highlight the statements that are considered by relatively high percentage of respondents (more than 18%) as totally unlikely:

13. *Protein chips are widely used by the public for personal use* (25.8% all respondents, 18.2% experts & knowledgeable)
17. *Living self-repairing abilities are implemented in artificial systems* (22.7% all respondents, 20% experts & knowledgeable)
14. *In vitro tests based on cells on chips replace animal testing* (18.8% all respondents, 20% experts & knowledgeable)

In addition, more than 10% of the respondents think that statements 3, 7, 9 and 18 will never be realized.

5. Impact of achievement

For each statement the respondents were asked to assess its impact if realized (*very high, high, low, negative*) on each of the following domains: science & technology, environment, life quality and the labor market. A domain impact index was calculated for each statement and domain, based on the following values: *very high=100, high=60, low=20, negative= -20*. An overall impact index for each statement was also calculated (mean value of the domain indices), which indicates the impact of each statement on all domains (for the calculation method see Appendix 2). Both indexes are shown in table 5. In Graph 4 the statements are ranked by the overall impact index, and the individual impact indexes are shown as well.

Table 5: Impact index
(top 3 highlighted in each domain)

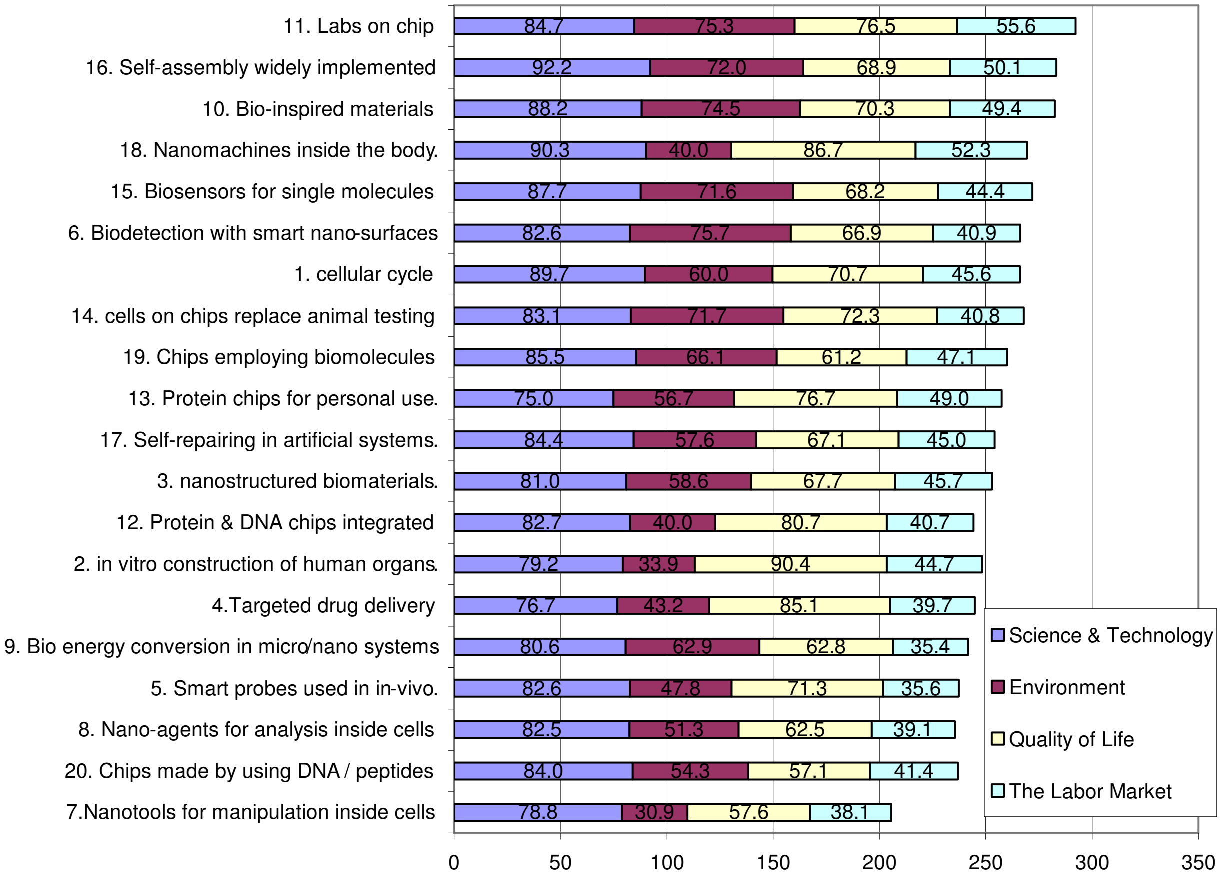
Statement	N	S&T	Environ ment	Life quality	Labor Market	Over all
1. cellular cycle	72	**89.7**	60.0	70.7	45.6	67.1
2. in vitro construction of human organs.	48	79.2	33.9	**90.4**	44.7	62.6
3. nanostructured biomaterials.	62	81.0	58.6	67.7	45.7	63.6
4.Targeted drug delivery	72	76.7	43.2	85.1	39.7	61.7
5. Smart probes used in in-vivo.	40	82.6	47.8	71.3	35.6	59.9
6. Biodetection with smart nano-surfaces	53	82.6	**75.7**	66.9	40.8	67.4
7.Nanotools for manipulation inside cells	35	78.8	30.9	57.6	38.1	50.9
8. Nano-agents for analysis inside cells	48	82.5	51.3	62.5	39.1	59.4
9. Bio energy conversion in micro/nano systems	31	80.6	62.9	62.8	35.4	61.4
10. Bio-inspired materials	35	88.2	**74.5**	70.3	49.4	**70.8**
11. Labs on chip	47	84.7	**75.3**	76.5	**55.6**	**72.7**
12. Protein & DNA chips integrated	30	82.7	40.0	**80.7**	40.7	62.9
13. Protein chips for personal use.	24	75.0	56.7	76.7	49.0	64.6
14. cells on chips replace animal testing	26	83.1	71.7	72.3	40.8	66.8
15. Biosensors for single molecules	39	87.7	71.6	68.2	44.4	68.8
16. Self-assembly widely implemented	46	**92.2**	72.0	68.9	**50.1**	**71.7**
17. Self-repairing in artificial systems.	18	84.4	57.6	67.1	45.0	64.1
18. Nanomachines inside the body.	30	**90.3**	40.0	**86.7**	**52.3**	68.9
19. Chips employing biomolecules	34	85.5	66.1	61.2	47.1	65.1
20. Chips made by using DNA / peptides	30	84.0	54.3	57.1	41.4	59.1

N=number of respondents

Evidently, the respondents' opinion is that the highest impact of most statements is on science and technology in general. In most statements the impact on the labor market is much lower then the impacts on S&T, environment and life quality, which is the main reason that the overall index is lower than the domain indexes.

Statements with highest ***overall*** impact are: 11- **Labs on chip**, 16- **Self-assembly** and 10- **Bio-inspired materials**.
Statements with highest impact on S&T are: 16- **Self-assembly,** 18- **Nanomachines in the body** and 1- **understanding cellular cycle**.
Statements with highest impact on the environment are: 11- **Labs on chip,** 10- **Bio-inspired materials** and 6- **Biodetection with smart nano-surfaces**.
Statements with highest impact on the quality of life are: 2- in vitro construction of human organs, 12-**Protein & DNA chips integrated**, and 18- **Nanomachines in the body**.
Impact on the labor market is generally low. Statements with highest impact on the labor market (over 50%, but much lower than other areas) are: 11- **Labs on chip**, 16- **Self-assembly** and 18- **Nanomachines in the body**.

It is noteworthy that the theranostic nanomachines (statement 18), although considered "visionary" (to be realized in 2025) is perceived as having relatively high impact on three domains: science & technology, life quality and the labor market.



Graph 4: Impact levels of all statements on the four domains. The statements are ranked according to the overall (mean) impact index (table 6).

Statements with adverse impact

According to a minority (up to 12%) of respondents (1 to 3 per statement), the realization of some statements will have adverse impact on the environment or the labor market, as shown in Table 6 and Table 7. No respondent foresaw an adverse impact on science and technology, and only one respondent ascribed an adverse impact on life quality to only one statement (No. 1: understading cellular cycle).

Table 6: Adverse impact on environment
(N= total respondents; N_a =number of respondents ascribing adverse impact)

Statement	N	N_a
12. Protein & DNA chips integrated	26	2
18. Nanomachines inside the body.	24	1
20. Chips made by using DNA / peptides	28	1
1. cellular cycle	67	2
7.Nanotools for manipulation inside cells	33	1
5. Smart probes used in in-vivo.	36	1
2. in vitro construction of human organs.	43	2
8. Nano-agents for analysis inside cells	46	2
3. nanostructured biomaterials.	56	2
4.Targeted drug delivery	62	1

Table 7: Adverse impact on the labor market
(N= total respondents; N_L =number of respondents ascribing adverse impact)

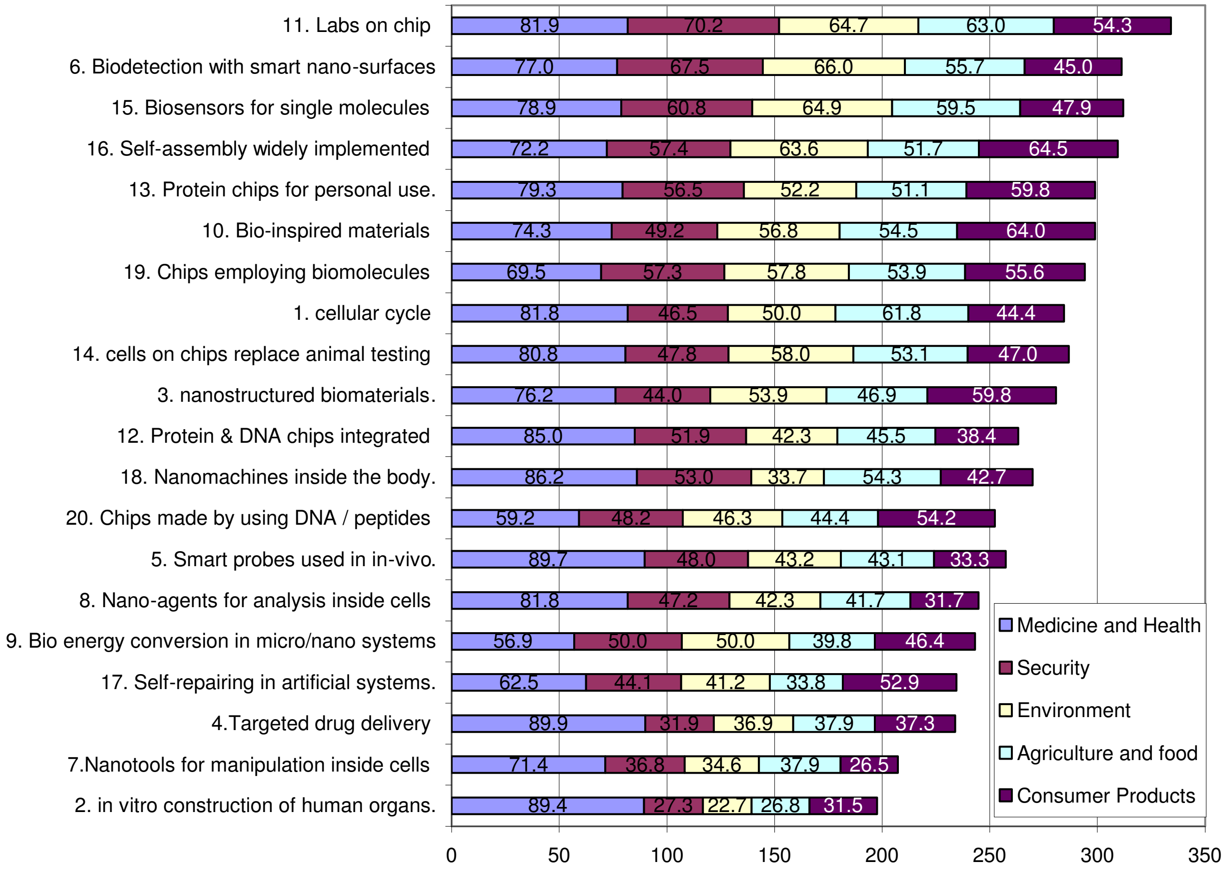
Statement	N	N_L
9. Bio energy conversion in micro/nano systems.	26	3
12. Protein & DNA chips integrated	27	2
17. Self-repairing in artificial systems.	15	1
2. in vitro construction of human organs.	47	3
14. cells on chips replace animal testing	25	1
20. Chips made by using DNA / peptides	28	1
4.Targeted drug delivery	65	2
1. cellular cycle	66	2
7.Nanotools for manipulation inside cells	33	1
5. Smart probes used in in-vivo.	35	1

6. Prospects of commercialization

For each statement the respondents were asked to assess its prospects of commercialization (*very high, high, low, impossible*) in each of the following application areas: health & medicine, security, environment, agriculture & food, and consumer products. An area-oriented prospect index was calculated for each statement and area, based on the following values: *very high=100, high=50, low=25, impossible=0*. An overall impact index for each statement was also calculated (mean value of the area indices), which indicates the commercialization prospects of each statement in all areas (for the method of calculation see Appendix 2). Both indexes are shown in table 8. In Graph 5 the statements are ranked by the overall impact index.

Table 8: Prospects of commercialization index
(top 3 highlighted in each area)

Statement	Medicine & Health	Security	Environment	Agriculture & Food	Consumer Products	Overall
1. cellular cycle	81.8	46.5	50.0	**61.8**	44.4	57.9
2. in vitro construction of human organs.	**89.4**	27.3	22.7	26.8	31.5	39.3
3. nanostructured biomaterials.	76.2	44.0	53.9	46.9	**59.8**	56.1
4.Targeted drug delivery	**89.9**	31.9	36.9	37.9	37.3	47.2
5. Smart probes used in in-vivo.	**89.7**	48.0	43.2	43.1	33.3	50.3
6. Biodetection with smart nano-surfaces	77.0	**67.5**	**66.0**	55.7	45.0	**62.9**
7.Nanotools for manipulation inside cells	71.4	36.8	34.6	37.9	26.5	41.8
8. Nano-agents for analysis inside cells	81.8	47.2	42.3	41.7	31.7	49.0
9. Bioenergy conversion in micro/nano systems	56.9	50.0	50.0	39.8	46.4	48.5
10. Bio-inspired materials	74.3	49.2	56.8	54.5	**64.0**	60.3
11. Labs on chip	81.9	**70.2**	**64.7**	**63.0**	54.3	**67.1**
12. Protein & DNA chips integrated	85.0	51.9	42.3	45.5	38.4	53.9
13. Protein chips for personal use.	79.3	56.5	52.2	51.1	**59.8**	60.4
14. cells on chips replace animal testing	80.8	47.8	58.0	53.1	47.0	57.8
15. Biosensors for single molecules	78.9	**60.8**	**64.9**	**59.5**	47.9	**62.4**
16. Self-assembly widely implemented	72.2	57.4	63.6	51.7	**64.5**	61.3
17. Self-repairing in artificial systems.	62.5	44.1	41.2	33.8	52.9	47.3
18. Nanomachines inside the body.	86.2	53.0	33.7	54.3	42.7	52.8
19. Chips employing biomolecules	69.5	57.3	57.8	53.9	55.6	58.7
20. Chips made by using DNA / peptides	59.2	48.2	46.3	44.4	54.2	51.0



Graph 5: Commercialisation prospects in the five application areas.
The statements are ranked according to the overall (mean) prospect index (table 9).

For all statements, Medicine & Health is the area that exhibits highest prospects for commercialization, with 9 topics scoring more than 80%. (It is noteworthy that even statement 20, a nanoelectronics topic, scores more in this area than in other areas.) The other four areas scored much lower prospect indexes.
Some topics in the security area, focusing on detection & identification, seem to have relatively higher prospects (>60%): *11- lab on chip, 6-biodetection, and 15-biosensors*. The same topics have the highest prospects in the environment area.

7. Statements mapped by overall impact and overall prospects of commercialization

In Graph 6 all the statements are mapped by their *overall* impacts and prospects. The likely time-frames of realisation are shown as well for completeness.
It can be observed that for most statements there is a positive correlation between the overall impact and overall prospects: statements with higher impact usually also have higher prospects of commercialization. The top five statements (having highest combination of overall impact and prospects indexes) are shown in Table 9.

Graph 6: Map of overall impact and prospects (all statements)

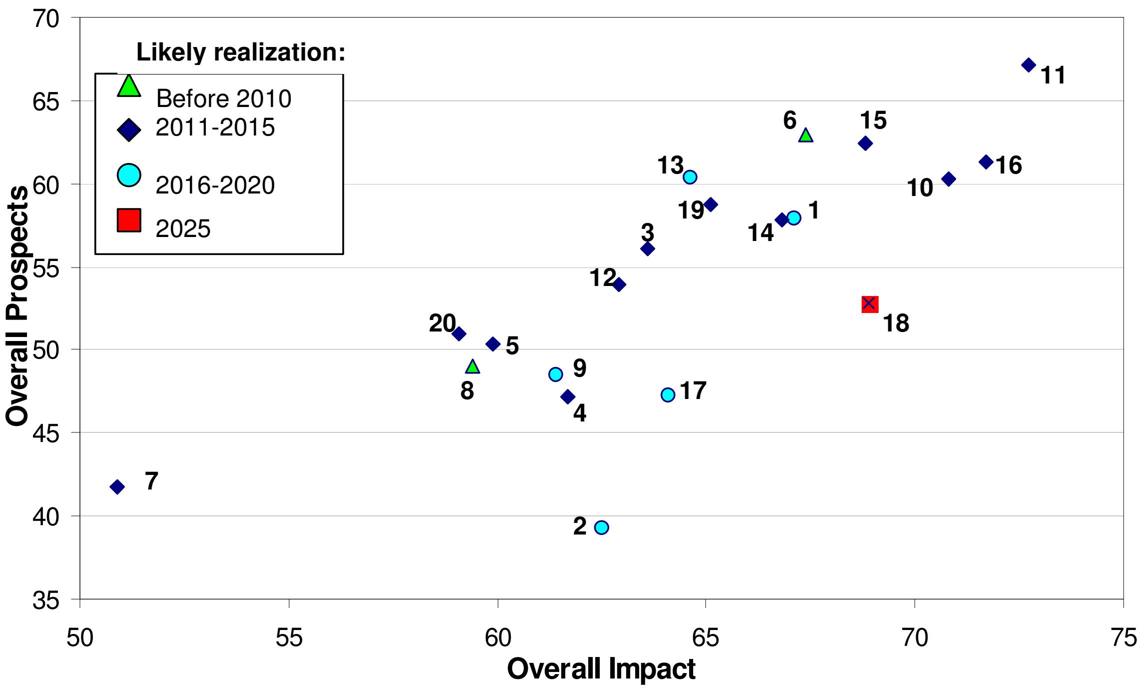


Table 9: Top 5 statements with highest combination of overall impact and overall commercialization prospects:

Statement	Impact	Prospects
11. Labs on chip are widely used for various applications, in different sectors, including households.	72.7	67.1
16. Self-assembly is widely implemented as a technique for development of materials and devices.	71.7	61.3
10. Advanced bio-engineered materials based on bio-inspiration/bio-mimicry are widely used.	70.8	60.3
15. Biosensors for detection of single molecules based on nano arrays (for example, arrays of nanotubes) are commercially available.	68.8	62.4
6. Smart and adaptable surfaces at the nanoscale are the basic building block for Biodetection.	67.4	62.9

Statements considered as impossible to commercialize:

Some statements are considered (by minority of respondents) as impossible to commercialize in certain areas. In the health & medicine area, the percentage of "impossible" is negligible for all statements (zero in 13 statements, <3.4% in 7 statements).

Statements with relatively high percentage (over 8%) of "impossible" in the other areas are:

- **In the security area**: statements 4-drug delivery (20%) , 2- in-vitro const. of organs (19%), 5-smart probes (11%), 9 (11%), 8 (9%), 7 (9%), 14, (9%).
- **In the environment area**: statements 2- in-vitro const. of organs (23%), 4-drug delivery (17%), 5- smart probes (13%), 12 (11%), 8, 13, 18 (9%).
- **In the agro-food area**: statements 2- in-vitro const. of organs (21%), 5, 9 (11%), 8 (9%)
- **In the consumer products area**: statements 2- in-vitro const. of organs (17%), 5-smart probes (17%), 18-theranostic nanomachines (13%), 12 (11%), 7, 8 (9%), 14, 4 (8%).

8. What limits the prospects of commercialization

For each technology statement the respondents were asked to assess what are the causes that limit the prospects of commercialization in each of the application areas mentioned in the preceding section. The optional answers were: *no needs, needs already fulfilled by other technologies, many barriers, or – "nothing limits"*.

Tables 10-15 present the percentage of the optional answers, for each statement and each application area.

Table 10: Percentage of "nothing limits" in all areas (top three highlighted in each area)

Statement	Medicine & Health	Security	Environment	Agro-food	Consumer Products
1. Cellular cycle	35.9	27.6	34.5	28.8	26.3
2. In vitro construction of human organs.	22.0	11.1	8.6	11.8	20.0
3. Nanostructured biomaterials.	44.2	29.2	40.4	31.8	**40.4**
4.Targeted drug delivery	42.1	18.0	16.3	23.4	24.4
5. Smart probes used in in-vivo.	39.4	26.7	30.0	35.7	22.2
6. Biodetection with smart nano-surfaces	**51.2**	**57.5**	**57.9**	**51.4**	**42.9**
7.Nanotools for manipulation inside cells	29.6	20.0	16.0	12.5	9.1
8. Nano-agents for analysis inside cells	40.5	29.0	34.4	26.7	25.9
9. Bio energy conversion in micro/nano systems	21.7	14.3	22.7	22.7	23.8
10. Bio-inspired materials	20.7	29.2	44.4	25.9	37.0
11. Labs on chip	**42.1**	**47.1**	**45.7**	**47.6**	**44.7**
12. Protein & DNA chips integrated	**45.8**	40.0	35.3	42.1	35.0
13. Protein chips for personal use.	26.3	33.3	26.3	26.3	29.4
14. cells on chips replace animal testing	38.9	38.9	40.0	**44.4**	33.3
15. Biosensors for single molecules	24.1	37.0	31.0	27.6	21.4
16. Self-assembly widely implemented	28.6	**45.7**	36.1	31.4	33.3
17. Self-repairing in artificial systems.	21.4	38.5	28.6	35.7	21.4
18. Nanomachines inside the body.	28.6	15.0	5.0	10.0	10.5
19. Chips employing biomolecules	29.2	43.5	**47.8**	43.5	39.1
20. Chips made by using DNA / peptides	14.3	9.5	10.0	10.0	4.6

It is evident from Table 10 that two statements are outstanding: high percentage of respondents think that nothing limits the commercialization of **Labs on Chip** (statement 11) and of **Biodetection with smart nano-surfaces** (statement 6) in ***all*** areas of application.
However, it is important to note that this opinion is *not consensual*: many respondents think that there are many barriers that limit the commercialization of the same statements.

Table 11: Limits to commercialization - Medicine & Health (%)
(large disagreements highlighted)

Statement	Nothing limits	Many barriers	Needs already fulfilled	No needs
1. cellular cycle	35.9	56.3	6.3	1.6
2. in vitro construction of human organs.	22.0	75.6	2.4	0
3. nanostructured biomaterials.	**44.2**	**36.5**	17.3	1.9
4.Targeted drug delivery	**42.1**	**50.9**	7.0	0
5. Smart probes used in in-vivo.	39.4	57.6	3.0	0
6. Biodetection with smart nano-surfaces	51.2	37.2	11.6	0
7.Nanotools for manipulation inside cells	29.6	63.0	7.4	0
8. Nano-agents for analysis inside cells	40.5	54.1	5.4	0
9. Bio energy conversion in micro/nano systems	21.7	60.9	13.0	4.3
10. Bio-inspired materials	20.7	51.7	13.8	13.8
11. Labs on chip	**42.1**	**44.7**	13.2	0
12. Protein & DNA chips integrated	**45.8**	**45.8**	8.3	0
13. Protein chips for personal use.	26.3	52.6	15.8	5.3
14. cells on chips replace animal testing	**38.9**	**44.4**	11.1	5.6
15. Biosensors for single molecules	24.1	62.1	10.3	3.4
16. Self-assembly widely implemented	28.6	65.7	2.9	2.9
17. Self-repairing in artificial systems.	21.4	78.6	0	0
18. Nanomachines inside the body.	28.6	71.4	0	0
19. Chips employing biomolecules	29.2	58.3	8.3	4.2
20. Chips made by using DNA / peptides	14.3	42.9	33.3	9.5

In Tables 11-15 it is easy to identify the degree of agreement among the respondents regarding the limits to commercialization. A comparable (and relatively high) percentage of "nothing limits" and "many barriers" indicates **large disagreement**. Conversely, large difference between the percentages of "nothing limits" and "many barriers" indicates **high degree of consensus** (for example in statement 17).

It is clear from Table 11 that in the medicine & health area a considerable disagreement on the limits to commercialization exists regarding the following statements:
3. Nanostructured biomaterials.
4.Targeted drug delivery
11. Labs on chip
12. Protein & DNA chips integrated
14. Cells on chips replace animal testing

Relatively high consensus exists in statements 2, 9, 17, 18.

Statements with especially high percentage of "many barriers" are:
17. Self-repairing in artificial systems (78.6%)
2. in vitro construction of human organs (75.6%)
18. Theranostic nanomachines inside the body (71.4%)

The number of "no need" responses is negligible for most statements, and the number of "needs already fulfilled by other technologies" is also very low. Hence, most respondents agree that these technologies, once realised, will find their niche in the health & medicine market and will meet existing and future needs.

Table 12: Limits to commercialization - Security (%)
(large disagreements highlighted)

statement	Nothing limits	Many barriers	Needs already fulfilled	No needs
1. cellular cycle	27.6	36.2	15.5	20.7
2. in vitro construction of human organs.	11.1	25.0	5.6	58.3
3. nanostructured biomaterials.	29.2	16.7	27.1	27.1
4.Targeted drug delivery	18.0	16.0	12.0	54.0
5. Smart probes used in in-vivo.	**26.7**	**26.7**	13.3	33.3
6. Biodetection with smart nano-surfaces	57.5	12.5	12.5	17.5
7.Nanotools for manipulation inside cells	20.0	16.0	4.0	60.0
8. Nano-agents for analysis inside cells	**29.0**	**29.0**	6.5	35.5
9. Bio energy conversion in micro/nano systems	14.3	42.9	14.3	28.6
10. Bio-inspired materials	29.2	20.8	16.7	33.3
11. Labs on chip	47.1	29.4	20.6	2.9
12. Protein & DNA chips integrated	40.0	15.0	10.0	35.0
13. Protein chips for personal use.	33.3	22.2	27.8	16.7
14. cells on chips replace animal testing	**38.9**	**27.8**	5.6	27.8
15. Biosensors for single molecules	**37.0**	**33.3**	7.4	22.2
16. Self-assembly widely implemented	45.7	28.6	11.4	14.3
17. Self-repairing in artificial systems.	**38.5**	**30.8**	0	30.8
18. Nanomachines inside the body.	15.0	40.0	0	45.0
19. Chips employing biomolecules	29.2	30.4	21.7	4.3
20. Chips made by using DNA / peptides	14.3	28.6	38.1	23.8

The commercialization in the security area seems to be questionable for most statements, except 2-labs on chip and 6-biodetection, which have both small percentages of "no needs" and relatively large percentages of "nothing limits".

Similar situation is observed in the area of environment (Table 13) and agriculture & food (Table 14). In the agro-food area, statement 1 (understanding cellular cycle) has very small percentage of "no needs", but in the same time it has relatively large percentage of "many barriers".

The commercialization in the consumer products area also seems to be uncertain. Again, statements 9, 16, 17 and 19 have relatively low percentage of "no needs" but relatively high percentage of "many barriers".

Table 13: Limits to commercialization - Environment (%)
(large disagreements highlighted)

Statement	Nothing limits	Many barriers	Needs already fulfilled	No needs
1. cellular cycle	**34.5**	**32.8**	19.0	13.8
2. in vitro construction of human organs.	8.6	11.4	5.7	74.3
3. nanostructured biomaterials.	40.4	25.5	19.1	14.9
4.Targeted drug delivery	16.3	26.5	6.1	51.0
5. Smart probes used in in-vivo.	**30.0**	**26.7**	13.3	30.0
6. Biodetection with smart nano-surfaces	57.9	23.7	7.9	10.5
7.Nanotools for manipulation inside cells	16.0	32.0	4.0	48.0
8. Nano-agents for analysis inside cells	34.4	21.9	9.4	34.4
9. Bio energy conversion in micro/nano systems	22.7	45.5	18.2	13.6
10. Bio-inspired materials	44.4	25.9	14.8	14.8
11. Labs on chip	45.7	28.6	5.7	20.0
12. Protein & DNA chips integrated	35.3	17.6	11.8	35.3
13. Protein chips for personal use.	**26.3**	**26.3**	15.8	31.6
14. cells on chips replace animal testing	**40.0**	**40.0**	40.0	20.0
15. Biosensors for single molecules	31.0	41.4	17.2	10.3
16. Self-assembly widely implemented	36.1	47.2	8.3	8.3
17. Self-repairing in artificial systems.	28.6	42.9	14.3	14.3
18. Nanomachines inside the body.	5.0	40.0	0	55.0
19. Chips employing biomolecules	47.8	30.4	13.0	8.7
20. Chips made by using DNA / peptides	10.0	30.0	40.0	20.0

Table 14: Limits to commercialization - Agriculture & Food (%)
(large disagreements highlighted)

Statement	Nothing limits	Many barriers	Needs already fulfilled	No needs
1. cellular cycle	28.8	49.2	18.6	3.4
2. in vitro construction of human organs.	11.8	17.6	5.9	64.7
3. nanostructured biomaterials.	31.8	40.9	13.6	13.6
4.Targeted drug delivery	**23.4**	**27.7**	17.0	31.9
5. Smart probes used in in-vivo.	35.7	21.4	17.9	25.0
6. Biodetection with smart nano-surfaces	51.4	17.1	14.3	17.1
7.Nanotools for manipulation inside cells	12.5	37.5	8.3	41.7
8. Nano-agents for analysis inside cells	**26.7**	**23.3**	16.7	33.3
9. Bio energy conversion in micro/nano systems	22.7	36.4	18.2	22.7
10. Bio-inspired materials	25.9	40.7	11.1	22.2
11. Labs on chip	47.6	35.3	2.9	14.7
12. Protein & DNA chips integrated	42.1	26.3	10.5	21.1
13. Protein chips for personal use.	**26.3**	**31.6**	26.3	15.8
14. cells on chips replace animal testing	44.4	22.2	11.1	22.2
15. Biosensors for single molecules	27.6	34.5	10.3	27.6
16. Self-assembly widely implemented	31.4	45.7	5.7	17.1
17. Self-repairing in artificial systems.	35.7	42.9	7.1	14.3
18. Nanomachines inside the body.	10.0	35.0	15.0	40.0
19. Chips employing biomolecules	43.5	30.4	13.0	13.0
20. Chips made by using DNA / peptides	10.0	20.0	45.0	25.0

Table 15: Limits to commercialization- consumer products (%)
(large disagreements highlighted)

Statement	Nothing limits	Many barriers	Needs already fulfilled	No needs
1. cellular cycle	26.3	35.1	21.1	17.5
2. in vitro construction of human organs.	20.0	25.7	8.6	45.7
3. nanostructured biomaterials.	40.4	27.7	23.4	8.5
4.Targeted drug delivery	24.4	15.6	11.1	48.9
5. Smart probes used in in-vivo.	22.2	33.3	7.4	37.0
6. Biodetection with smart nano-surfaces	42.9	25.7	11.4	20.0
7.Nanotools for manipulation inside cells	9.1	22.7	9.1	59.1
8. Nano-agents for analysis inside cells	**25.9**	**25.9**	3.7	44.4
9. Bio energy conversion in micro/nano systems	23.8	52.4	14.3	9.5
10. Bio-inspired materials	37.0	29.6	14.8	18.5
11. Labs on chip	44.7	26.3	7.9	21.1
12. Protein & DNA chips integrated	35.0	15.0	10.0	40.0
13. Protein chips for personal use.	**29.4**	**35.3**	17.6	17.6
14. cells on chips replace animal testing	**33.3**	**33.3**	0	33.3
15. Biosensors for single molecules	21.4	35.7	7.1	35.7
16. Self-assembly widely implemented	33.3	45.5	12.1	9.1
17. Self-repairing in artificial systems.	21.4	64.3	7.1	7.1
18. Nanomachines inside the body.	10.5	47.4	0	42.1
19. Chips employing biomolecules	**39.1**	**34.8**	17.4	8.7
20. Chips made by using DNA / peptides	4.6	45.5	27.3	22.7

9. Actions needed to enhance the likelihood of realization

For each statement the respondents were asked what actions are needed to enhance the likelihood of realization.
The optional answers were: *increase in basic research, increase in applied research, financial measures, regulations (including standards), solution of ethical problems,* and *promoting public acceptance*. The results are shown in the following table.

Table 16: Actions needed to foster realization*

Statement	N	Increase in basic/ applied research	financial measures	Regula tion	Solve ethical problems or public acceptance
1. cellular cycle	78	79.5	17.9	20.5	38.5
2. in vitro construction of human organs.	50	78.0	22.0	36.0	**62.0**
3. nanostructured biomaterials.	65	81.5	26.2	32.3	24.6
4.Targeted drug delivery	73	82.2	24.7	39.7	39.7
5. Smart probes used in in-vivo.	40	**90.0**	22.5	37.5	32.5
6. Biodetection with smart nano-surfaces	53	88.7	15.1	20.8	11.3
7.Nanotools for manipulation inside cells	38	86.8	15.8	7.9	28.9
8. Nano-agents for analysis inside cells	51	84.3	17.6	19.6	37.3
9. Bio energy conversion in micro/nano systems	32	84.4	25.0	15.6	28.1
10. Bio-inspired materials	36	**88.9**	19.4	25.0	22.2
11. Labs on chip	49	87.8	24.5	36.7	28.6
12. Protein & DNA chips integrated	31	80.6	25.8	48.4	35.5
13. Protein chips for personal use.	31	64.5	19.4	22.6	32.3
14. cells on chips replace animal testing	32	68.8	18.8	37.5	37.5
15. Biosensors for single molecules	42	88.1	28.6	26.2	16.7
16. Self-assembly widely implemented	46	**91.3**	19.6	15.2	17.4
17. Self-repairing in artificial systems.	20	85.0	15.0	25.0	**50.0**
18. Nanomachines inside the body.	35	85.7	25.7	22.9	**57.1**
19. Chips employing biomolecules	40	75.0	15.0	22.5	20.0
20. Chips made by using DNA / peptides	35	82.9	25.7	8.6	17.1

The prevalent opinion among the respondents is that the most important action to enhance the likelihood of realization for all statements is increase in basic/applied research – especially in statements 5, 6, 10 and 16.
Surprisingly, fiscal/financial measures are considered by most respondents as least needed action.
Regulation activity is needed especially in statement 12-Protein & DNA chips integrated (48.4%). For all other statements less than 40% of the respondents recommend regulation activities.
Solution of ethical problems and public acceptance issues is needed to enhance the realisation likelihood of several statements, especially statement 2 (in vitro construction of human organs), statement 18 (theranostic nanomachines inside the body), and statement 17 (living self-repairing abilities in artificial systems).

* Percentages don't add up to 100% because more then one action could be checked.

10. Comments of respondents

In the questionnaire the respondents were invited to add free comments on the statements. Only few chose to do so. Their comments are presented below.

1. cellular cycle

- Cellular cycle knowledge is the key to develop biosensors
- My answer mainly concerns the perspective of biotechnology (the nano or micro is in this sense meaningless)
- Nanobiotechnology will play some role in understanding cell cycles, but will not be the only (nor key) technology needed.
- Statement may be true if and only if nanobiotechnology is not simply considered as a set of techniques
- The major problem will be the increase in basic research, since this is not covered by most granting agencies. Second comment is related to the R&D in industry, which is oriented to the short-term financial success, less to middle-term ones.
- we must overcome a common public misconception that all scientific cellular research originates from/involves stem cells derived from human embryos

2. in vitro construction of human organs

- It is a worrisome topic. It may be misused widely.
- Nanobiotechnology will contribute, but will not be the key technology, unless of course basic transport phenomena at the small scale (which have been studied since the late 1800s but are still not completely understood)
- regenerative medicine is one of the most important breakthrough direction of research in medicine today and it advances with the highest speed
- The prospect of artificial non biological nano-or micro devices replacing some specialist cell functions is within reach (insuline producing devices etc). The real stuff and full organs will come much later from better understanding of cell growth.
- Tissue engineering does not belong to bionanotechnolgy in my opinion. It involves cell biolgy and chemistry (biopolymers) and material sciences . AFM and quantum dots will be used as a tool.

3. Novel nanostructured biomaterials replace existing materials

- Nano is not perse better than not nano or multi nano - biomaterials might be better than other materials for some purposes - in medicine or in environment
- Some new materials will come out of nano-bio, and some of these will replace synthetic polymers. Engineered biopolymers (whose engineering does not always involve nano) are already replacing synthetic polymers in some applications (e.g., PHA)
- Ethical problems and public acceptance will be depending on innovations in basic research/novel discoveries and their R&D.
- Micro arrays technology and nanosized labels can be seen as a area of bionanotechnolgy. In vivo nanostructres may find some applications.

4. Targeted drug delivery based on nanoparticles becomes a standard tool

- Why based on nano particles? - The promise of decades of immunological research was also targeted drug delivery - if we fully understand the immunological differentiation and complexity needed for this, we might develop enough target specific recognition for any disease (with no need for nano targeted particles)
- It's the real source for innovative medicine nowadays.
- Liposomes are used since decades as “nanoparticles”;. The problems of drug targeting are only weakly related to the size. Thus bionanotechnolgy contributes only to low extent to the specificity and stability problems.

5. Smart probes (that illuminate when reaching their target) are practically used in diagnosis in-vivo

- Smart probes that operate at the nanoscale already exist. For example, many fluorescent dyes fluoresce only when they attach to certain target molecules (e.g., DNA). Of course, the dyes are molecules, i.e., they are a few nanometers big.
- To substitute MRI and radio-labeled vectors by optical will be difficult and not very important.

6. Smart and adaptable surfaces at the nanoscale are the basic building block for Biodetection.

- This tool might be used in basic research to detect changes on nano level in living cells so a tool for basic (biophysical research) - other applications are really very hard to visualise for biodetection there will be a large array of other technologies.
- For bioanalysis nanotechnolgy is not needed. For research single molecule detection and for sensors surface optimization using nanotools and nanomaterials is interesting.
- Many biosensors use membranes as interface to detect the targeted species.
- Products already available today but slow market acceptance.
- the military should highly support reserach in this area and speed up implementation as it might help both: detection capabilities and reduce military activity impact on the invironment and human health
- There will be many fields of application and there are several items to improve, first the repeatability and accuracy of sampling and measure, then the data handling informatics, data mining etc needs to be user friendly when it will be fully developed.

7. Nanotools (e.g. optical tweezers) are used for manipulation inside cells while keeping the cells' integrity and activity

- It is a tool for basic research, I cannot see applications in other areas
- Are optical tweezers really nanotools? They were introduced well before the nanotechnology craze, and they work best on particles/objects that are around a micron in size (it's very hard to trap particles below a few hundred nanometers). Optical tweezers are extremely important tools, as are other non-invasive manipulation techniques.
- Nice tools, but not very important.

8. Nanosized imaging agents (e.g. quantum dots) are used for analysis and diagnosis inside cells without affecting their normal functionality.

- A nice tool for basic biophysical research. No other applications.
- Bionanotechnology contributes only in minor extent to the application of such agents. The immunological and toxicological effects are more related to surface chemistry than to the size.
- It will be a revolution in Science and Technology
- Requires significant financial and fiscal investment in quantum dot research. This new and emerging technology, maintaining the stability and reproducibility of image production inside living cells alongside simultaneous cell metabolism is a massive challenge.
- This is already being done!

9. Biological energy conversion systems (e.g. biomolecular motors) are practically used in artificial micro/nano systems.

- Here we deal with large uncertainties, but if feasible we can really have a revolutionary area. Not only motors but also all kind of computer devices might be assembled this way.
- Nice vision, low relevance

10. Advanced bioengineered materials based on bio-inspiration/bio-mimicry are widely used.

- What has this to do with bionanotechnology?
- I think that studying the strategies used by cells in a quantitative way gives an unique opportunity to design new devices. Biological systems offer a window into a very sophisticated collection of nanomachines.
- There are too many unknown factors in bio-inspiration and bio-mimicry that are hard to be reproduced in a quantitative manner for better understanding. Nature is complex.

- I consider this not as a nano specific statement, but a general one. We already learned a lot of biology, there is still a lot to be learned. Many natural designs can be used and adapted to serve our needs on all scale levels.

11. Labs on chip are widely used for various applications, in different sectors, including households

- Lab on chips is a logic step in miniaturising and automatising all kind of monitoring and diagnostic procedures - so this will be a good prospect of nano(bio)technology
- Price will decide over application. Multiplex analytical tools will be important. Engineering will be more important than nanotechnological aspects.

12. Protein chips are integrated with DNA chips for specific diagnosis purposes in current hospital practices.

- In basic research and diagnostics this might be a logic development – see statement 11
- Medical doctors acceptance and costs are strong factor.
- They are already in use!!
- This area is a major area to improve detection of cancer and survival rate!!
- What are the benefits?

15. Biosensors for detection of single molecules based on nano arrays (e.g arrays of nanotubes) are commercially available

- Many needs are already fulfilled by other technologies, but autonomous, portable and real-time devices are not yet available.
- Single molecule detection is nice, but not necessary for practical applications.
- Theoretically feasible, but not robust enough for a commercial product.

16. Self-assembly is widely implemented as a technique for development of materials and devices

- Self-assembly is a popular term these days. I am interpreting it in a very strict sense, that of deliberately-engineered (designed) self-assembly, as opposed to discovered self-assembly.
- Governments should provide sufficient research and developments funds in this development. The return will be great.
- Integration of applied and fundamental research required
- Item interpreted to include self-replication as well as self-assembly

17. Living self-repairing abilities are implemented in artificial systems

- Fields for applications uncertain. What you mean by living self-repair ability? DNA repair, self assembly processes, lipid bilayer fusion processes, protein-protein assemblies?
- I interpret this statement as referring to biology-based systems

18. Nano-machines for theranostics (therapy and diagnosis) are practically used inside the body

- The statement will occur during the 2020-2030 decade. Interpreted to refer to non-biological systems (e.g., diamondoid molecular machine systems)
- Enhancing self regeneration might perhaps be possible (like supporting bone after friction), but this is only support of therapy because the body restores the tissue
- The potential of nano-machines for diagnostics and therpeutics is limitless. Biological to digital converters, miniscules cameras, drug delivery carriers, tissue enhancers and blood oxygenerators are just few examples of the large potential.
- What are nanomachines? This is a buzzword and comprises many different things: polymeric vesicles, contractile proteins, virus capsules… From my experience (in a project aimed at developing nanoparticles to be used as MRI contrast agent), the immune system is very effective in scavenging particles from blood. The only "particles" which show long circulation times are liposomes.

19. Chips employing biomolecules as active elements are commercially manufactured

- Difficult to assess specific commercial potential, since such chips could vary widely in their nature (depending on the biomolecules, how they're used, etc.)
- The questions are time consuming and overlapping. Look at the lab on chip - this development might be parallel.
- What means “active elements”? Since proteins are widely used as bio-recognition elements on chips, this is already reality. Statement 19 is covered by statement 13.

20. Nanoelectronics chips are commercially manufactured by using DNA or peptides (as templates or for nanopatterning)

- A potentially powerful technology, but one that goes against current trends. The resistance of large companies to switch to a fundamentally new technology may be significant.
- Interesting concept but academic. No commercial relevance, as fulfilled by inorganic structures.
- Nanofabrication using DNA as templates will hardly find commercial applications. It is interesting for research.

12. Conclusions

1. The expert survey provides a worldwide view on selected future developments in Nanobiotechnology and their potential impacts and prospects in different domains, emerging from judgments of a large group of NBT experts.
2. Practical and commercial applications of NBT developments under consideration will be realized mainly in the area of **medicine and health**. In other areas practical use and commercialization are questionable or uncertain.
3. Much scientific research activity is still needed in order to develop the NBT field and to identify its potentially successful applications in different areas.
4. It seems that there are no critical limitations to the development of the field, except a few cases where issues of ethics and public acceptance are identified. Financial matters are not considered as a major obstacle.
5. The following topics are of high priority, taking into account their overall impact (on all domains considered) and their commercialization prospects (in all areas considered):
    - *Labs on chip* (statement 11)
    - *Self-assembly for materials and devices* (statement 16)
    - *Bio-engineered materials based on bio-inspiration/bio-mimicry* (statement 10)
    - *Biosensors for detection of single molecules based on nano arrays* (statement 15)
    - *Biodetection with smart nano-surfaces* (statement 6).
6. The highest impact of most statements is on science and technology in general. In most statements the impact on the labor market is much lower then the impacts on S&T, environment and life quality.
   Statements with highest impact on S&T are: 16- *Self-assembly*, 18- *Theranostic nanomachines in the body* and 1- *understanding cellular cycle*.
   Statements with highest impact on the environment are: 11- *Labs on chip*, 10- *Bio-inspired materials* and 6- *Biodetection with smart nano-surfaces*.
   Statements with highest impact on the quality of life are: 2- *in vitro construction of human organs*, 12-*Protein & DNA chips integrated*, and 18- *Theranostic nanomachines in the body*. The last statement, although considered "visionary" (realized in very long term), is perceived as having high impact on three (out of five) areas of application.

7. For all statements, Medicine & Health is the area that exhibits highest prospects for commercialization, with 9 topics scoring more than 80%. The other four areas scored much lower prospect indexes. Some topics in the security area, focusing on detection & identification, seem to have relatively higher prospects (>60%): 12- *lab on chip*, 6-*biodetection,* and 15-*biosensors.*

8. Topic with no limits to commercialization in ***all*** application fields, according to approx. half of the respondents, are *Labs on chip* (statement 11) and *Biodetection with smart nano-surfaces* (statement 6). However, the same topics are considered by ~40% of respondents as having "many barriers". This is one example of marked disagreements between the experts on several issues in this survey.

9. In the Medicine & Health area, statements with high percentage (>70%) of "many barriers" are: 17-*Self-repairing in artificial systems*, 2-*in vitro*

construction of human organs* and 18-*Theranostic nanomachines inside the body.*

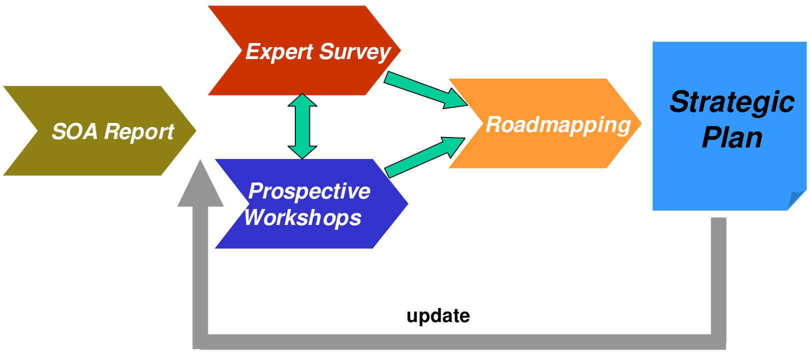
10. Most of the technology statements are likely to be realized till 2015 (detailed likely realization times are presented in Graph 3). Realization of two statements (6- *Biodetection with smart nano-surfaces*, and 8-*Nano-agents for analysis inside cells*) is forecasted in short term (before 2010). Twelve statements are likely to realize in medium term (2011-2015) and five statements in longer term (2016-2020). One particular statement, "*theranostic nanomachines practically used inside the body*" is considered as "visionary", with expected realization around 2025 (interestingly, the "experts" and "knowledgeable" respondents tend to be more optimistic, and expect the realization a few years earlier).

11. The prevalent opinion is that the most important action to enhance the likelihood of realization for all statements is increase in basic/applied research (with different degrees among the statements). Surprisingly, fiscal/financial measures are considered to be the least needed action (only 15%-29% of the experts recommend this action in all statements). Regulation activity is needed mainly in statement 12-*Protein & DNA chips integrated* (according to 48% of respondents) and in statement 4-*Targeted drug delivery* (40%). For all other statements less than 40% of the respondents recommend regulation activities. Solution of ethical problems and public acceptance issues is needed to enhance the realization of several statements, especially statement 2 (*in vitro construction of human organs*), statement 18 (*theranostic nanomachines inside the body*), and statement 17 (*living self-repairing abilities in artificial systems*).

12. It should be remembered that the current expert survey doesn't necessarily cover the *entire* NBT field. One could have added more topics, beyond the 20 statements selected for this survey. In such expanded and more comprehensive survey different conclusions might have emerged.

13. What next?

The expert survey is one of the activities in the foresight and strategy task of N2L. These activities should complement each other and be coordinated in order to lead to the final goal – the strategic plan for the network and the forthcoming ENBI*. This coordinated effort is depicted in the following scheme.



* The European Nanobiotechnology Institute

It should be stressed that one of the main advantages of the expert survey is the possibility to acquire knowledge from a large number of experts, thereby reflecting the professional opinion of the relevant community. The results can then help stimulate further discussions in smaller groups such as prospective workshops which, even though much dependent on the limited number of participants, can sharpen and deepen the future-oriented thinking and give rise to additional insights.

Foresight is a *continuous* process, and an expert survey must be followed by additional discussions and other activities.
Some future activities could follow the present survey:

- Running a second round in order to achieve a higher degree of agreement (a common practice in such foresight Delphi-type surveys)**,** especially on topics with low consensus, high percentage of "never" or topics with many barriers and/or public acceptance issues. This could also be achieved in part of the statements by means of brainstorming sessions and/or interviews with relevant specialists.
- It would be interesting to initiate international professional discussions on topics such as statement 17 (*Living self-repairing abilities implemented in artificial systems),* which has high disagreement on time of realization, high percentage of "never", high percentage of "many barriers" and high percentage of respondents who think that there is a need to solve ethics/public acceptance problems.
- Adding possibly missing topics and expanding the survey
- Stimulate discussions among N2L members on the results, in order to better shape the conclusions and provide useful inputs to N2L policy and programmes.

Appendix 1: Structure of the online survey

Statement9: Biological energy conversion systems (e.g. biomolecular motors) are practically used in artificial micro and nano systems.

A- Your level of expertise on this statement

- Expert
- Knowledgeable
- Familiar
- Unfamiliar

B- When will the statement occur ?

- Before 2010
- 2011 – 2015
- 2016 – 2020
- After 2020
- Never

C- What will be the level of impact of this achievement on the following domains:

(Please mark the appropriate box for each domain)

Science and Technology	Very high	High	Low	Negative
Environment	Very high	High	Low	Negative
Quality of Life	Very high	High	Low	Negative
The labor market	Very high	High	Low	Negative

D- What are the prospects of commercialization of this technology in the following areas:

(Please mark the appropriate box for each domain)

Medicine and Health	Very High	High	Low	Impossible
Security	Very High	High	Low	Impossible
Environment	Very High	High	Low	Impossible
Agriculture and Food	Very High	High	Low	Impossible
Consumer Products	Very High	High	Low	Impossible
Other (please specify) :				
	Very High	High	Low	Impossible

E- What limits the prospects of commercialization:

(Please make the appropriate selection for each domain)

Medicine and Health ------>

------>
Many barriers
No needs
Needs Already fulfilled by other technologies
Nothing limits

Security

Environment

Agriculture and Food ------>

Consumer products ------>

F- Actions needed to enhance the likelihood of the statement

(you can tick more than one : hold the ctrl-key while clicking)

Increase in basic research
Increase in applied R&D
Fiscal and financial measures
Regulations (e.g. standards)
Solve ethical problems
Public acceptance

G- Please submit comments you might have regarding this statement :

Appendix 2: Results calculation method

The questionnaire designed for the N2L expert survey included the following:
1. Personal information on the participants to collect data on their gender, their country of residency, their professional expertise, their affiliation and sectors to which they belong.
2. A list of 20 statements, each of them referring to an emerging development in nanobiotechnology. For each of these technologies the survey aimed to asses several issues:
The timeframe in which the statement will occur.
The level of its impact on four domains: science and technology, environment, quality of life, the labor market.
The prospects of commercialization of this technology in five different areas: medicine & health, security, environment, agriculture & food, consumer products.
The limitations on commercialization of the technology as assessed by the participant.
Actions needed to enhance the likelihood of the realization of the technology, as input to a long range policy in this field.

The answers were collected online, stored in a database and processed, enabling us to compare between the various statements and prioritize them, thus deriving insights on the development of nanobiotechnology in the next 20 years and its impact on science and technology, on the economy and on the quality of life.
In the following we describe the calculation of the quantitative survey results.

<u>When will the statement occur</u>
In order to calculate the median and quartiles for each statement the time frames were represented by the following:
Before 2010 ≡ 2008
2011 - 2015 ≡ 2013
2016 – 2020 ≡ 2018
after 2020 ≡ 2025

The answers for "Never" are presented separately and are not included in the calculations.

<u>The level of impact</u>
In order to grade the level of impact the following calculations were made (see table 1):

Impact Category / Domain	Very high (100)	High (60)	Low (20)	Negative (-20)	Mean
Science & Technology	I_{11}	I_{12}	I_{13}	I_{14}	MI_1
Environment	I_{21}	I_{22}	I_{23}	I_{24}	MI_2
Quality of life	I_{31}	I_{32}	I_{33}	I_{34}	MI_3
The labor market	I_{41}	I_{42}	I_{43}	I_{44}	MI_4

Table 1 – Impact of achievement

Each category was weighed as follows:
K_1 - Category 1 ≡ Very high ≡ 100
K_2 - Category 2 ≡ High ≡ 60
K_3 - Category 3 ≡ Low ≡ 20
K_4 - Category 4 ≡ Negative (adverse) ≡ -20

For each of the four domains a weighted mean MIi ($1 \le i \le 4$) was calculated.
If I_{ij} ($1 \le i \le 4$, ($1 \le j \le 4$) is the number of participants who chosed category j as the level of impact on domain i then MI_i, the weighted mean for domain i, is calculated as follows:

$$M_i \ (1 \le i \le 4) = \frac{I_{i1} x\ 100 + I_{i2}\ x\ 60 + I_{i3}\ x\ 20 + I_{i4}\ x(-20)}{S_i}$$

were $S_i = I_{i1} + I_{i2} + I_{i3} + I_{i4}$

The value of MI_i in this case will span from –20 (if all will chose the "Negative" Category) to 100 (if all will chose the "Very High" Category).
This calculation results in four different distributions for each of the four domains, ranking the 20 statements according to their level of impact on each domain.
In addition, an overall impact index was calculated as the mean of the individual weighted means of all participants.
So if participant n chose Category K_{in} for domain i then his mean M_{in} is
$M_{in} = (K_{1n} + K_{2n} + K_{3n} + K_{4n}) / N_k$

N_k is number of categories that were referred to by the participant. (In this case $2 \le N_k \le 4$).
In a case in which a Category was not chosen for a certain domain, then only the chosen ones were included in the calculation.
For each participant at least 2 domains had to be chosen in order to be included. (Some of the participants didn't refer to all questions).
The index of impact is then the sum of all individual means.
MI_n divided by the number of actual participants.

The prospects of Commercialization

In order to grade the prospects of commercialization of each technology the following calculation were made (see table 2).

Prospects Category / Area	Very high (100)	High (50)	Low (25)	Negative (0)	Mean
Medicine and Health	P_{11}	P_{12}	P_{13}	P_{14}	MP_1
Security	P_{21}	P_{22}	P_{23}	P_{24}	MP_2
Environment	P_{31}	P_{32}	P_{33}	P_{34}	MP_3
Agriculture and Food	P_{41}	P_{42}	P_{43}	P_{44}	MP_4
Consumer Products	P_{51}	P_{52}	P_{53}	P_{54}	MP_5

Table 2 – Prospects of commercialization

Each Category was weighted as follows:
C_1 Category 1 ≡ Very high ≡ 100
C_2 Category 2 ≡ High ≡ 50
C_3 Category 3 ≡ Low ≡ 25
C_4 Category 4 ≡ Impossible ≡ 0

For each five areas a weighted mean MP_i ($1 \le i \le 5$) was calculated.
If P_{ij} ($1 \le i \le 5$, $1 \le j \le 4$) is the number of participants who chosed Category j as the level of prospects of commercialization in area i then MP_i the weighted mean for area i will be calculated as follows:

$$MP_i\ (1 \le i \le 5) = \frac{I_{i1} \times 100 + I_{i2} \times 50 + I_{i3} \times 25}{S_i}$$

Where $S_i = I_{i1} + I_{i2} + I_{i3} + I_{i4}$

The value of Mpi will span from 0 (if all will chose the "Impossible" Category) to 100 (if all will chose the "Very High" Category).
This calculations result in five different distributions for each of the five areas ordering the 20 statement according to their prospects of commercialization in the five areas:
Medicine and Health, Security, Environment, Agriculture and Food, Consumer products.
In addition, an overall prospects index was calculated. This index is the mean of the individual weighted means of all participant. If participant n chosed Category K_{in} for area i then his mean MP_n is:

$$MP_n = (C_{1n} + C_{2n} + C_{3n} + C_{4n})/N_k$$

N_k is the number of categories that were referred to by the participant (In this case $3 \le N_k \le 5$).
If a category was not chosen for a certain area then only the chosen ones were included in the calculation. For each participant at least 3 areas had to be chosen in order to be included. (Some of the participants didn't refer to all areas). The index of prospects of commercialization is then the sum of all individual means MP_n divided by the number of actual participants.

Appendix 3: Example of detailed results (per statement)

Statement 2: Advancements in nanobiotechnology enable the construction in vitro of artificial human organs

Level of expertise			When will the statement occur?							
				All respondent		Experts and Knowledgeable		Familiar		χ^2
	N	%		N	%	N	%	N	%	
Expert	2	3.8	Before 2010	4	7.8	2	8.0	2	7.7	
Knowledgeable	24	46.2	2011-2015	15	29.4	7	28.0	8	30.8	**.63**
Familiar	26	50.0	2016-2020	12	23.5	7	28.0	5	19.2	**n.s**
	52	**100**	After 2020	16	31.4	7	28.0	9	34.6	
			Never	4	7.8	2	8.0	2	7.7	
				51	**100**	**26**	**100**	**25**	**100**	

	All Respondents						Experts and Knowledgeable						
	What will be the level of impact of this achievement on the following domains:												
Domain	N	Very high (100)	High (60)	Low (20)	**Negative (-20)**	**Mean[1]**	N	Very high (100)	High (60)	Low (20)	**Negative (-20)**	**Mean[1]**	[3]χ^2
		%	%	%	%			%	%	%	%		
Science and Technology	48	56.3	35.4	8.3	0	**79.2**	24	54.2	33.3	12.5	0	**76.7**	1.10
Environment	43	9.3	18.6	69.8	2.3	**33.9**	23	13.0	17.4	65.2	4.3	**35.7**	1.80
Quality of life	46	76.1	23.9	0	0	**90.4**	23	73.9	26.1	0	0	**89.6**	.119
The labor market	47	12.8	42.6	38.3	6.4	**44.7**	24	16.7	33.3	45.8	4.2	**45.0**	2.67
	What are the prospects of commercialization of this technology in the following areas												
Area	N	Very high (100)	High (50)	Low (25)	**Impossible (0)**	**Mean[2]**	N	Very high (100)	High (50)	Low (25)	**Impossible (0)**	**Mean[2]**	[3]χ^2
Medicine and Health	47	80.9	14.9	4.3	0	**89.4**	23	82.6	8.7	8.7	0	**89.1**	3.27
Security	43	7.0	7.0	67.4	18.6	**27.3**	21	4.8	4.8	76.2	14.3	**26.1**	1.46
Environment	43	2.3	7.0	67.4	23.3	**22.7**	22	4.5	9.1	63.6	22.7	**25.0**	1.34
Agriculture and Food	42	4.8	14.3	59.5	21.4	**26.8**	22	9.1	13.6	63.6	13.6	**31.8**	3.27
Consumer Products	42	7.1	21.4	54.8	16.7	**31.5**	22	9.1	22.7	54.5	13.6	**34.1**	.534

What limits the prospects of commercialization?											
	All Respondents					Experts and Knowledgeable					
Area	N	Many barriers	No Need	Need already fulfilled by other technology	**Nothing limits**	N	Many barriers	No Need	Need already fulfilled by other technology	**Nothing limits**	[3]χ^2
		%	%	%	%		%	%	%	%	
Medicine and Health	41	75.6	2.4	0	**22.0**	20	75.0	0	5.0	**20.0**	1.12
Security	36	25.0	58.3	5.6	**11.1**	20	30.0	55.0	5.0	**10.0**	.61
Environment	35	11.4	74.3	5.7	**8.6**	18	11.1	66.7	11.1	**11.1**	2.46
Agriculture and Food	34	17.6	64.7	5.9	**11.8**	17	23.5	52.9	11.8	**11.8**	3.39
Consumer Products	35	25.7	45.7	8.6	**20.0**	18	27.8	33.3	16.7	**22.2**	4.22

	All Respondents		Experts and Knowledgeable	
	N	%	N	%
Increase in basic research	50	56.0	25	60.0
Increase in applied R&D	50	60.0	25	60.0
Fiscal and financial measure	50	22.0	25	24.0
Regulations (e.g standards)	50	36.0	25	40.0
Solve ethical problems	50	50.0	25	40.0
Public acceptance	50	50.0	25	48.0