A REPORT ON THE BIOMATERIALS RESEARCH TRANSLATION IN EUROPE

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ESB

European Society for Biomaterials

40 years 1976-2016
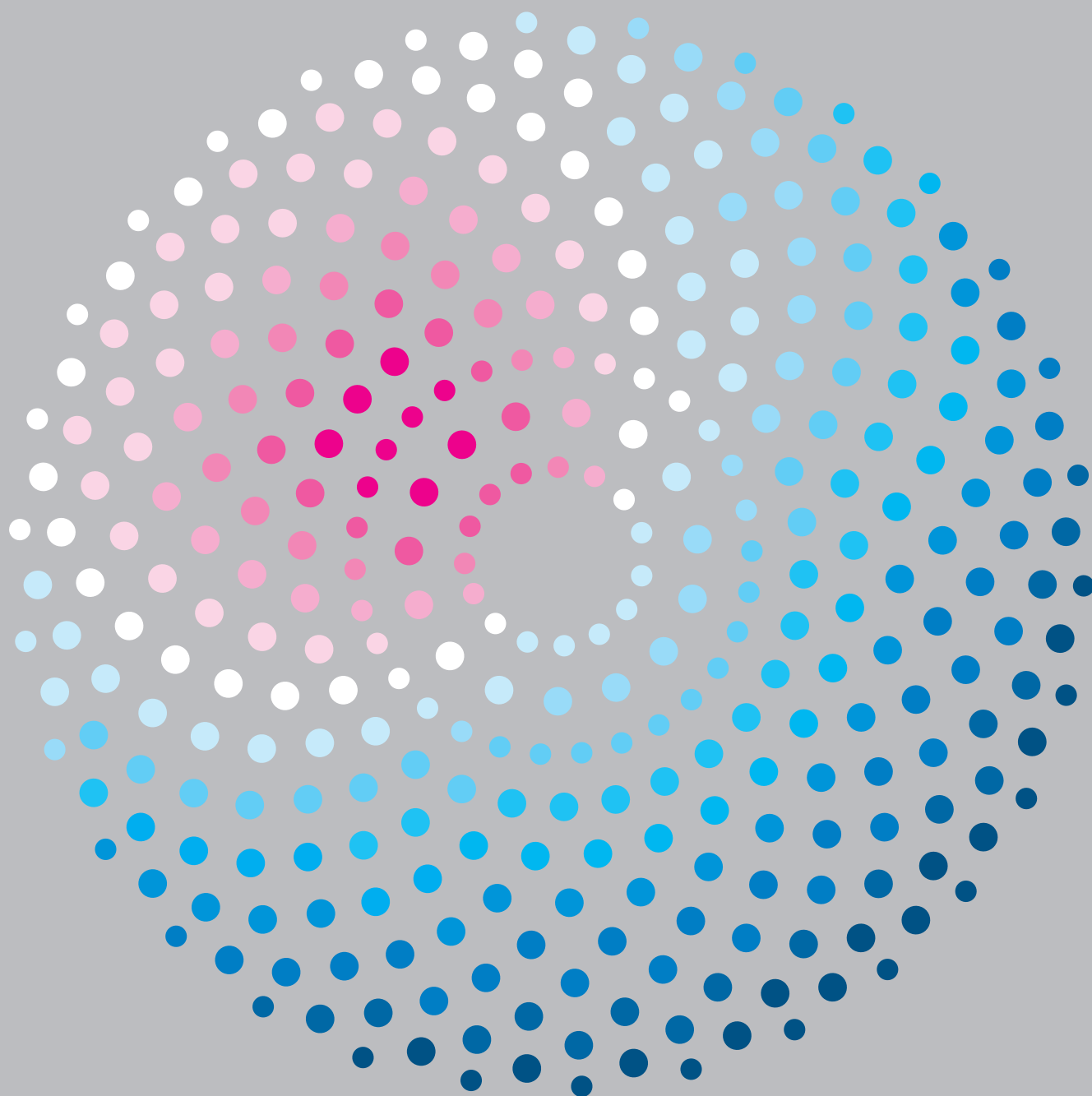
This report has been commissioned in 2014 by the ESB Council in collaboration with the Presidents of the national societies of biomaterials across Europe.

"Action without a name,
a who attached to it, is meaningless"

Hannah Arendt

The ESB President's Editorial

In 2014 I called a meeting of the Presidents of the National Societies for Biomaterials to put forward a proposal for a study assessing the state of biomaterials research translation in Europe. The meeting was held in Liverpool during our annual conference and I was glad to see a high attendance. The enthusiasm for the gathering and for this initiative was palpable; the Presidents were joined by representatives of their boards and ideas flew around the table about the scope of the study, the methodology and the format to be used and obviously about the final objectives.

We all agreed that the main scope of the study should be to present the ESB community in all its richness, potential and cohesiveness to the various stakeholders. We wanted to make our presence felt as a resource for all those involved in medical innovation. We wanted to present ourselves as a community of technopreneurs; innovative minds able to pioneer new technology, experts able to understand the needs of industry and determined to assist companies in the resolution of problems, responsible professionals capable of informing and influencing policy makers and regulatory bodies. We wanted to be recognised as a cohesive community open to collaboration, uniquely bonded in our intents for over forty years. We wanted to map our research and our facilities to help industry to find innovation, consultancy and state-of-the-art facilities across Europe. We wanted to assess, in a manner as objective as possible, the state-of-the-art of biomaterials research translation in Europe, identifying sources of funding and investments, research trends, success stories and gaps to be filled.

We all agreed to invest part of the available ESB budget for the commissioning of a report that could be supported by measureable data and factual evidences. The modus operandi was clear to us all. We decided to set the project in different phases:

• Find European experts in socio-economical analyses of biomedical research translation who would be able to assist us in the collection of data through an ad hoc designed questionnaire and who would be able to expertly analyse them.

• Make sure that the questionnaire would cover the widest possible geographical area and range of research organisations in Europe.

• Direct the questionnaire mainly at research team leaders to minimise duplication of information from same teams as much as possible.

• Map facilities while respecting the anonymity of the respondents

• Present the results in a concise and reader-friendly format.

A six-month search led to the identification of INGENIO, CSIC-Universitat Politècnica de València, Spain, a research group with a well-established expertise in this type of studies in the biomedical arena. We would like to thank the INGENIO group leaders Dr Pablo D'Este and Dr Davide Consoli and their collaborator Dr Francois Perruchas for embracing the project with so much enthusiasm and for competently driving us throughout the process and patiently listening to our opinions and integrating our feedback in the final paper.

We thank the European Technological Platform on Nanomedicine and the Biomaterials Committee – Medical Device Division, Institute of Materials, Minerals and Mining for helping us to disseminate the questionnaire among their members.

Later in the project, it became evident that the report would benefit from the opinion of experts in biomaterials across Europe and beyond. Under the leadership of Prof Yannis Missirilis and Prof Maria Vallet-Regi we collected opinion leaders' papers written by renowned scientists. These complement the report as an invaluable source of advice for all and a source of inspiration for the new generation of scientists and technopreneurs. Our deepest gratitude goes to Prof Missirilis and Prof Vallet-Regi as well as to all the prestigious group of scientists who responded to their invitation, Prof Luigi Ambrosio, Prof James Kirkpatrick, Prof Liisa Kuhn, Prof Josep Planell, Prof Buddy Ratner, Prof Julie Scholes and Prof David Williams.

Our thanks also go to Mr Will Nice, Brenton Blue, UK for sealing the information of this report with a beautiful design that so deeply represent the spirit of the ESB community.

Last but not least, our deep sense of gratitude is for all the members of the ESB as their trust and support has made the achievement of this project possible. The results here shown are a testimony to the work of so many individuals and groups who believe that biomaterials will be at the forefront of the technology enabling medical innovation in the years to come. Among the many information made available, this report shows the added value of the networking, the increasing number of projects focussing on biomaterials for regenerative medicine, the numerous projects that have reached the stage of clinical validation and commercial exploitation. The work of many years is indeed coming into fruition to the benefit of the European industry.

Gaps still need be filled, fast tracks to innovation need to be found and the lack of participation of the public in the debate and in the scientists' and policy makers' choices needs to be addressed. However, the fertile ground on which stakeholders can nurture the future of medical devices and regenerative medicine products clearly emerges from this study. We hope that this will be a useful tool for the reader who cares about public health and the success of our industry. We hope the report will be a guide and a source of inspiration for young scientists and entrepreneurs.

On behalf of the ESB Council and of the Presidents of the National Societies for Biomaterials across Europe.
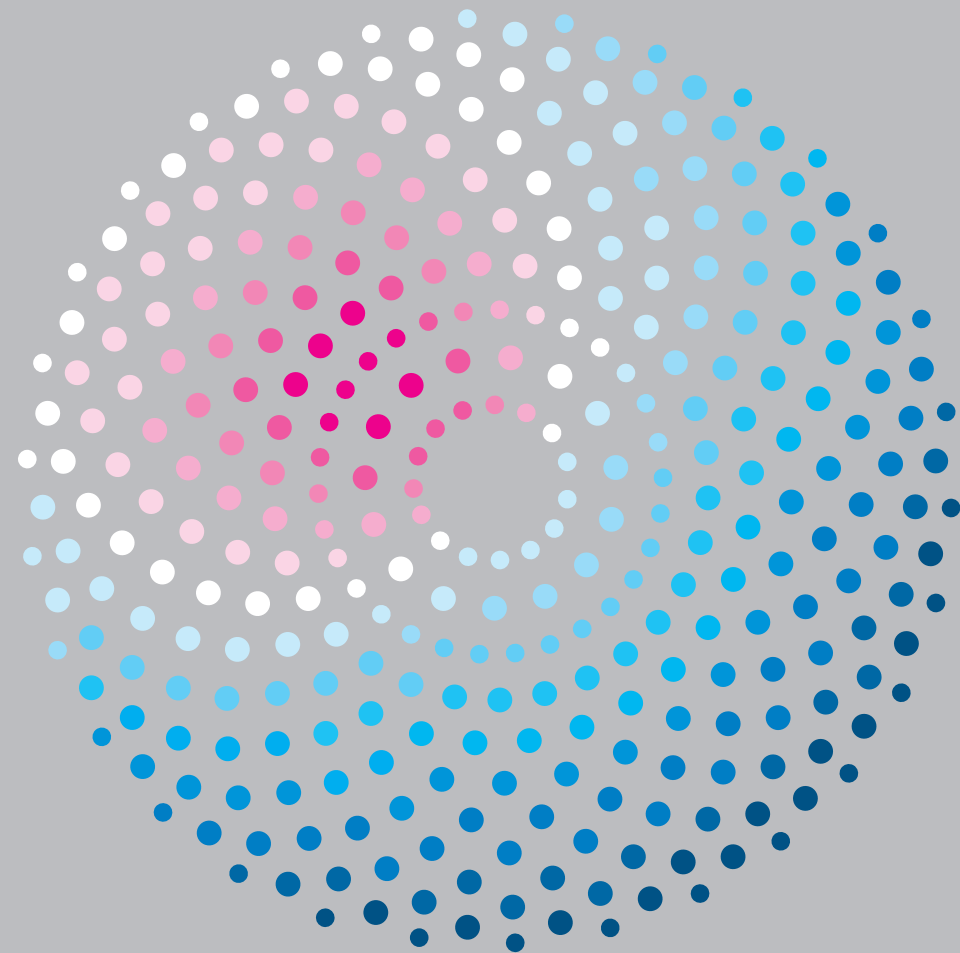
Prof Matteo Santin,

ESB President
(September 2013-September 2017)

Report: Biomaterials Stakeholders and Research in Europe

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1. Preamble

This report is based on 201 complete responses to a questionnaire circulated to key stakeholders of Biomaterials Science in Europe between October 2016 and January 2017. The document is organized as follows. The first section includes descriptive information about the surveyed population. While no inference is made in this part of the report, the descriptive evidence aims at providing a schematic overview of the characteristics of respondents across three dimensions: geographical, professional and scientific. The second section of the report presents an analysis of the research activities carried out within the European Society for Biomaterials. Using projects as unit of analysis allows us to capture the structure and the outcomes of interactions between respondents and their network of collaborators. In the same spirit, the last part of the report presents an empirical analysis of the key regularities that characterize these network activities.

2. Descriptive Evidence

2.1. Data collection

To reach respondents, the president of the European Society for Biomaterials (ESB) sent an invitation letter which was distributed by each of the national contact points of the ESB. The letter included a URL which permitted ESB members to fill the questionnaire online. All respondents to the survey remain anonymous. Information about the national contact point and country from where respondent filled the questionnaire is obtained via the URL and the geolocation of the respondent's access to internet (IP address). Therefore, in this report the respondent's country is inferred from the national contact point and not from the country of residence. In the very few cases where the national contact point information was missing, we used the country obtained from the IP address. Table 1 and Figure 1 summarize the geographical distribution of respondents.

Figure 1.
Breakdown of responses by country

Table 1. Breakdown of responses by country

* Scandinavia includes respondents from Norway, Sweden and Finland.

	Number of responses
Belgium	10
France	12
Germany	13
Greece	16
Ireland	6
Italy	17
Netherlands	17
Poland	13
Portugal	4
Romania	29
Scandinavia*	5
Spain	11
Switzerland	8
Turkey	11
United Kingdom	27
Total	201

2.1. Individual respondents

Respondents were asked about their scientific background, i.e. the field of their highest academic qualification (e.g. PhD degree). The results show two macro groups of countries:

The dominant field of specialization (i.e. between 26% and 80% of respondents) is Biomaterials: this is the case of (in decreasing order) Scandinavia, Portugal, Greece, France, Ireland, Poland, Turkey and the United Kingdom.

Fields other than Biomaterials have the largest shares, i.e. Medicine in Romania (34%), Chemistry in Belgium (40%), Biomedicine in Italy (24%), Chemistry and Biology in Germany (23%). Switzerland stands out as the country with the most diversified portfolio of academic disciplines among respondents.

Table 2.
Scientific background of the respondents – by country

- Biochemistry
- Biology
- Biomaterials
- Biomedical Engineering
- Biomedical Sciences
- Chemistry (polymer, organic, inorganic, …)
- Material Engineering
- Medicine
- Other
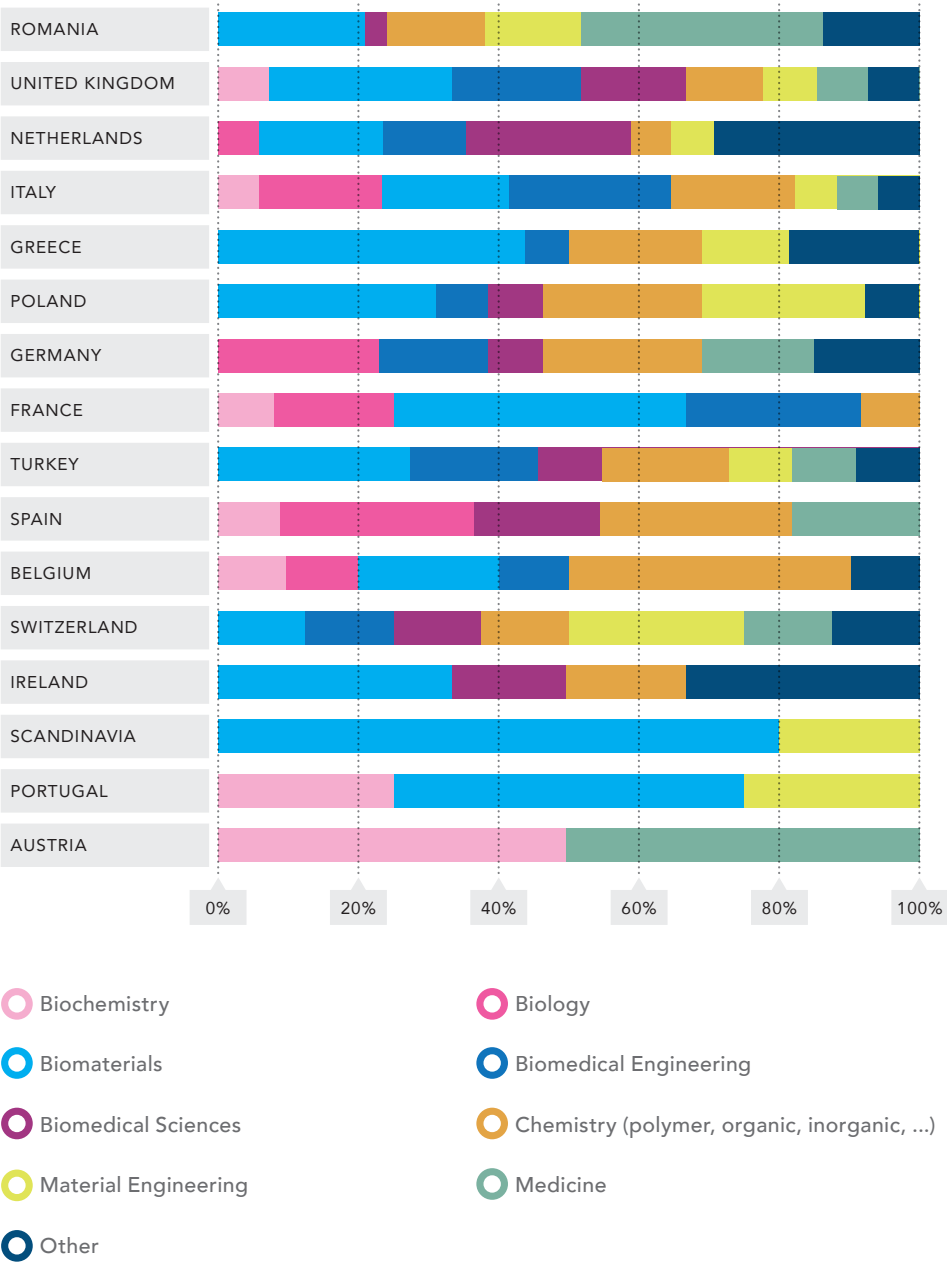
Figure 2. Respondents' affiliation — by type

Looking at the type of affiliation, in most of the countries Universities hold a clear majority among respondents, with a range that varies between 100% in Poland to 54% in the United Kingdom. There is a second group of countries where Universities have either only a small majority (i.e. Spain with 44% followed by 33% of University Hospitals), have no majority (i.e. Germany 39% together with Public/Private Research Laboratory) or a minority (i.e. Portugal and France where the dominant affiliation type is Public or Private Research Laboratory – 66% and 50% respectively).
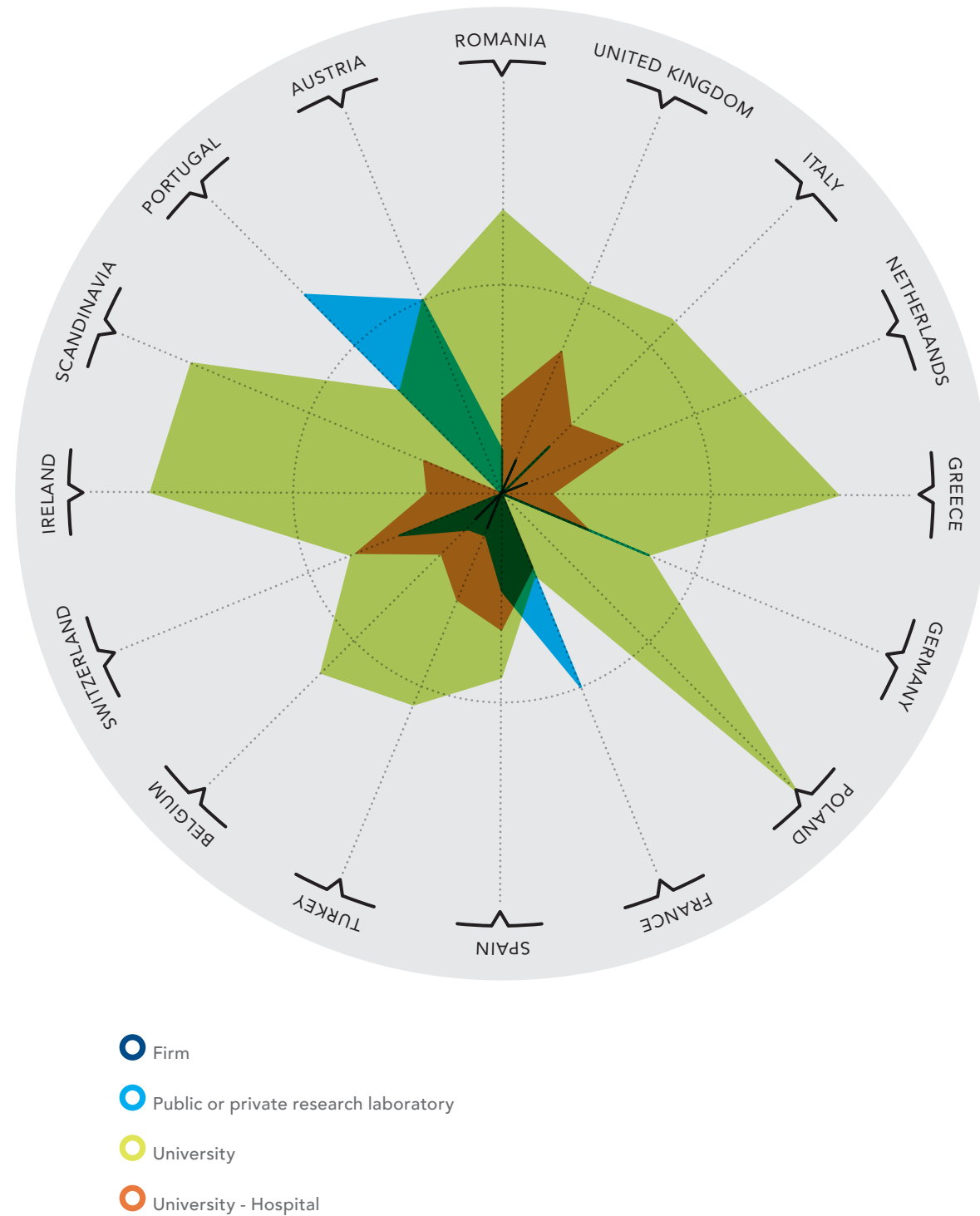
Figures 3 to 6 display the geographical distribution of respondents by type of organizational affiliation: University (Figure 3), University-Hospital (Figure 4), Public or Private Research Laboratory (Figure 5) and Firm (Figure 6).

Figure 3. Geographical distribution of organizations across Europe: Universities

- ● Firm
- ● Public or private research laboratory
- ● University
- ● University - Hospital

19

6.65 AVERAGE

1
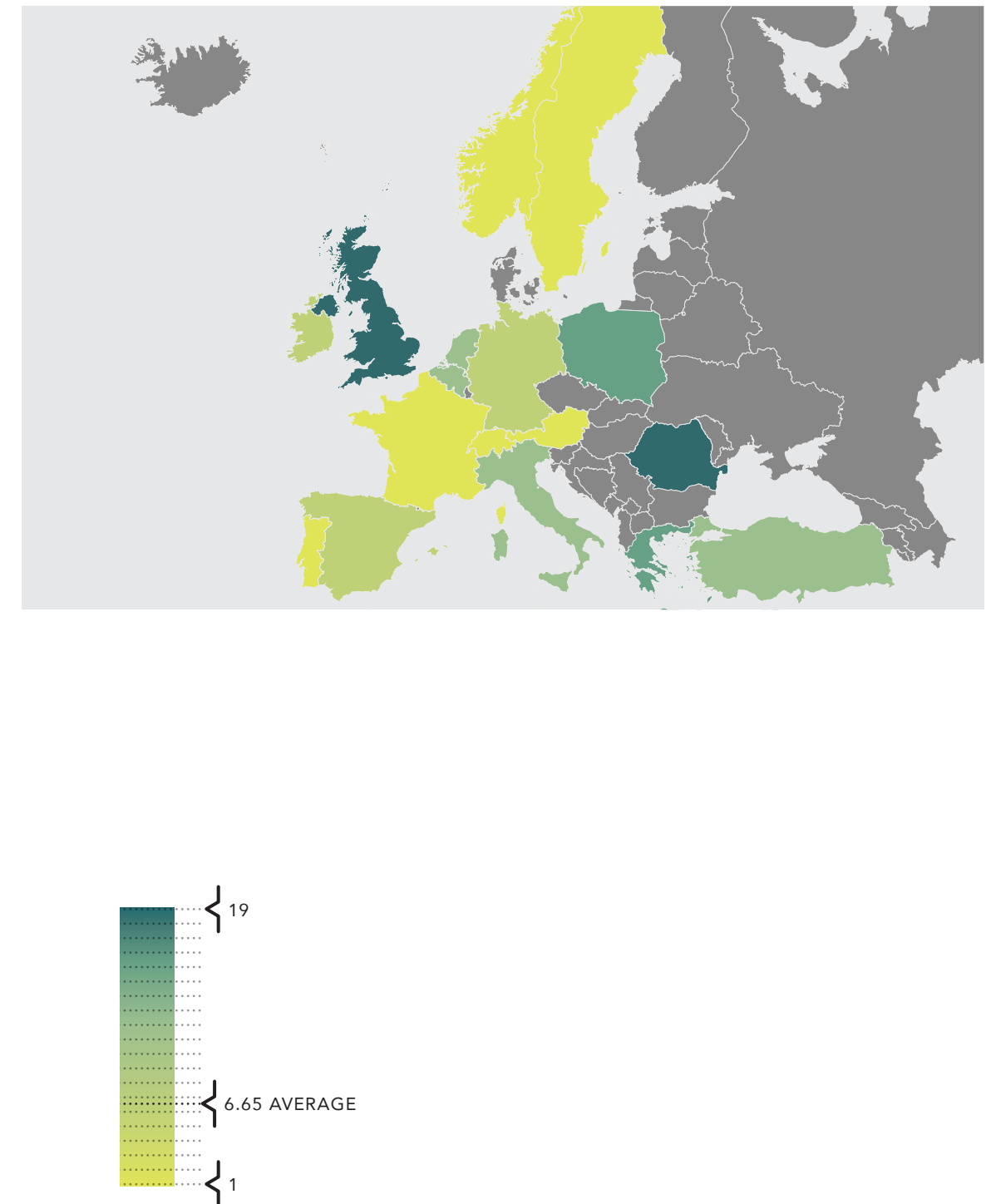
Figure 4.

Geographical
distribution of
organizations across
Europe: University –
Hospital

10

3.29 AVERAGE

1
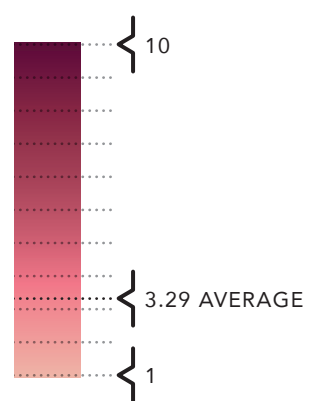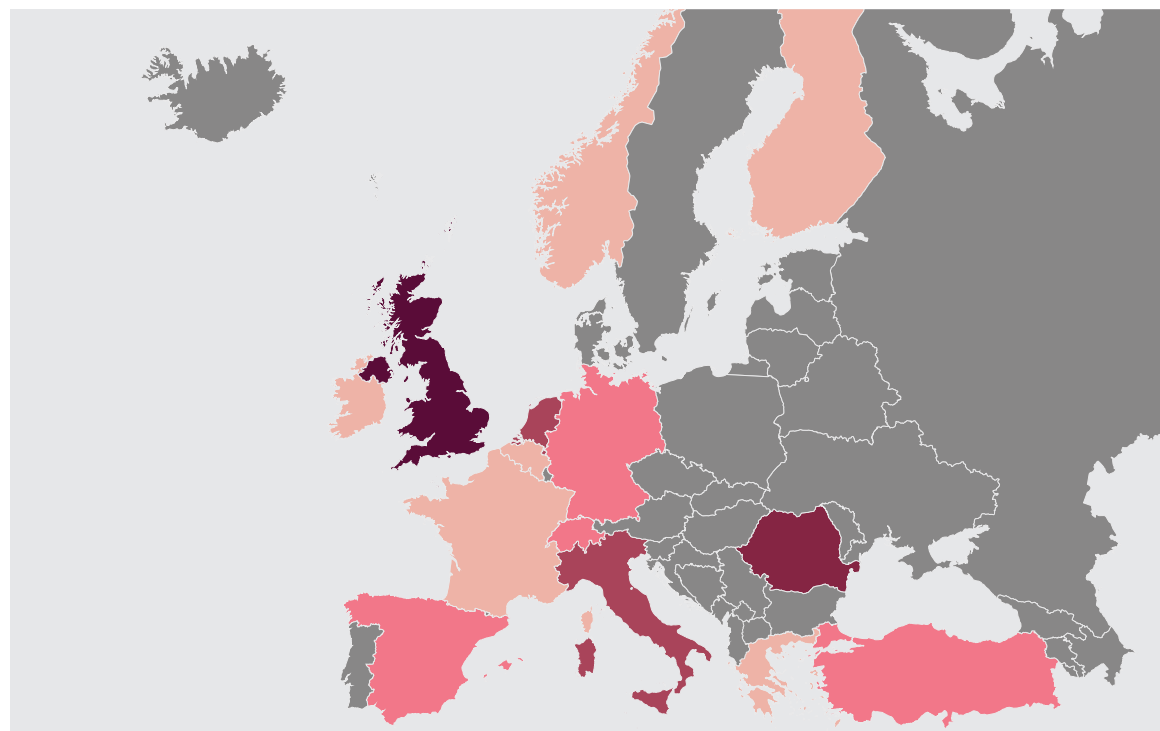
Figure 5.

Geographical
distribution of
organizations across
Europe: Research
Laboratory

5

2.36 AVERAGE

1
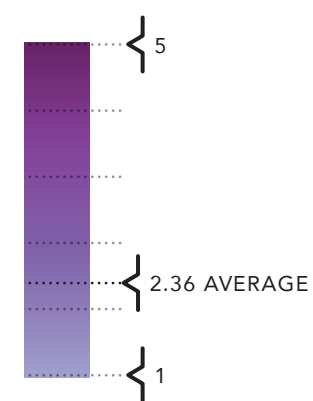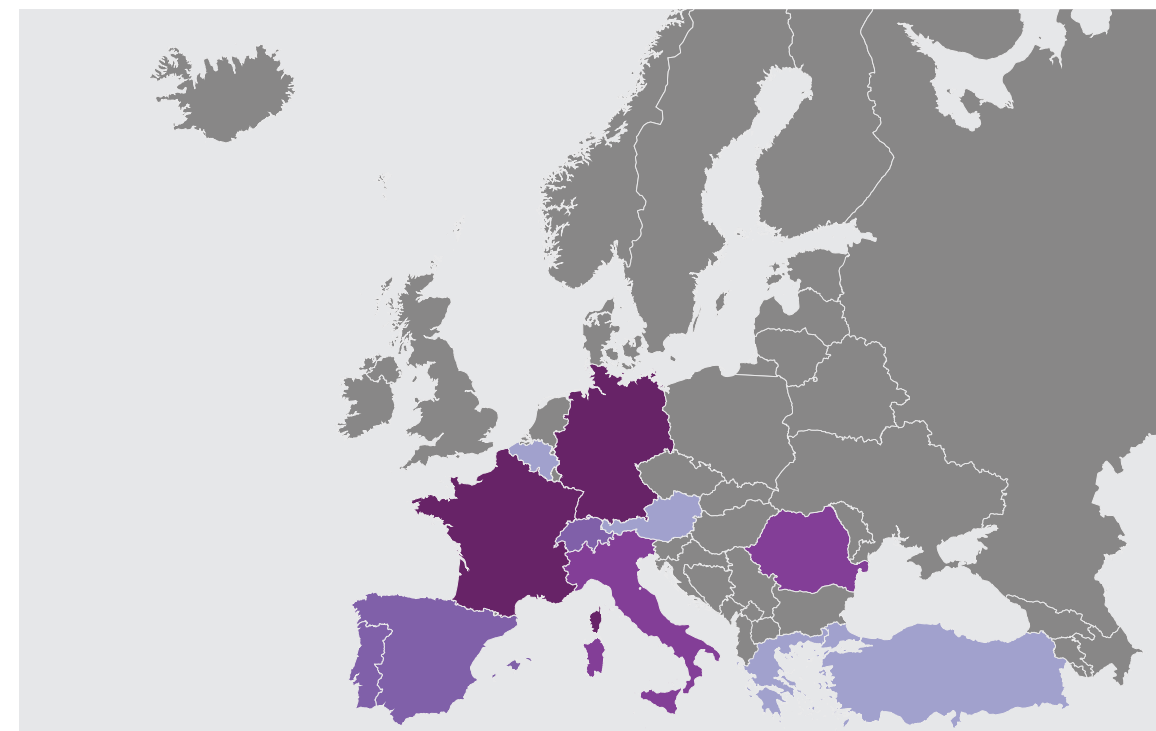
Figure 6.
Geographical distribution of organizations across Europe: Firm
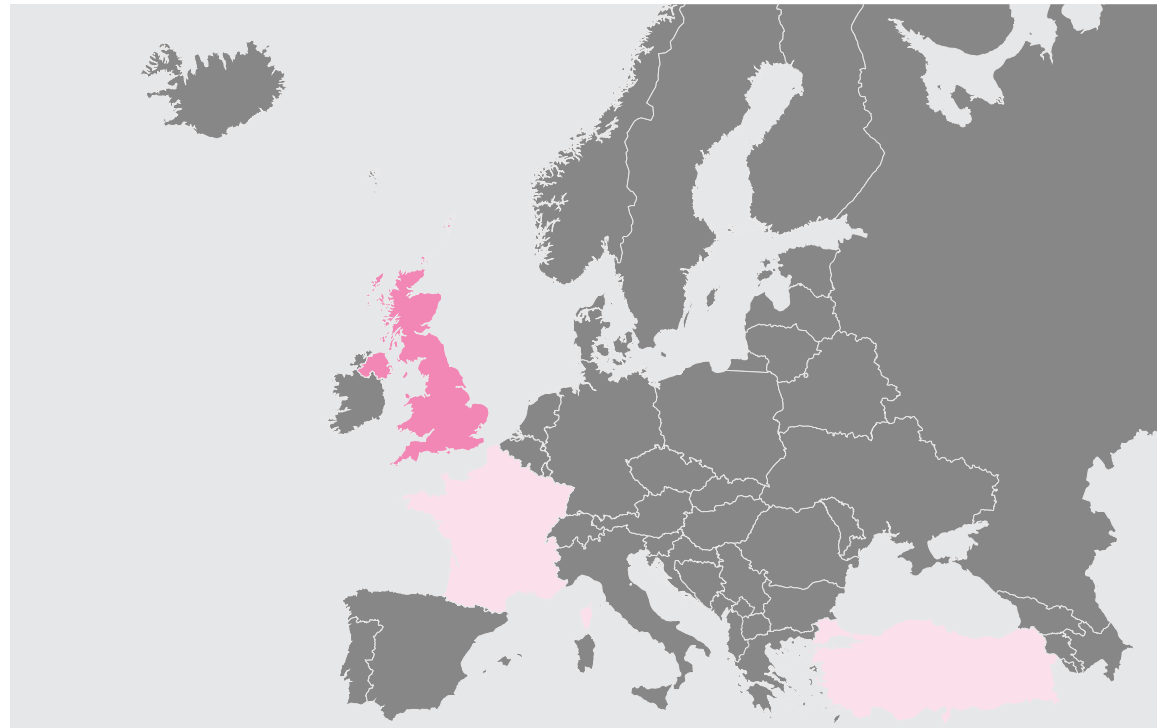
Looking at the job title of respondents, three categories stand out as making up for 68% of the sample: Full Professors (30%), Associate Professors (22%) and Senior Researchers (16%).

5

1.2 AVERAGE

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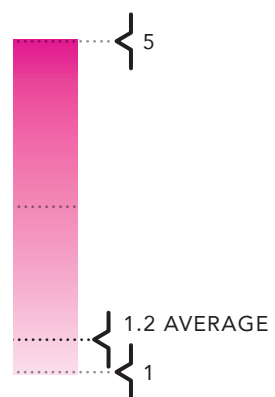
Figure 7.
Job title – all countries

- Full Professor
- Senior Researcher
- Associate Professor
- Research Fellow
- Associate / Lecturer
- PhD Student
- Other

2.2. The distribution across countries highlights three groups of countries:

1. Full professors hold the lion share in Romania, Belgium, UK, Greece and France as well as Poland and Scandinavia – jointly with Associate professors;
2. Senior Researchers have the majority of respondents in Italy, Germany and Ireland (between 50% and 30%), Associate Professors stand out in Spain (47%) and Switzerland (31%);
3. Countries with a very balanced set of professional profiles: Netherlands, Portugal, Turkey. Germany 39% together with Public/Private Research Laboratory) or a minority (i.e. Portugal and France where the dominant affiliation type is Public or Private Research Laboratory – 66% and 50% respectively).

Figure 8.
Job title — by country

Respondents were asked about the number of years since the first employment. The majority, about 38%, had between 11-20 years of work experience in their field.

Figure 8 — Job title by country, stacked bar chart.

Countries (top to bottom): ROMANIA, UNITED KINGDOM, NETHERLANDS, ITALY, GREECE, POLAND, GERMANY, FRANCE, TURKEY, SPAIN, BELGIUM, SWITZERLAND, IRELAND, SCANDINAVIA, PORTUGAL, AUSTRIA

X-axis: 0%, 20%, 40%, 60%, 80%, 100%

Legend:
- Full Professor
- Senior Researcher
- Associate Professor
- Research Fellow
- Associate / Lecturer
- PhD Student
- Other
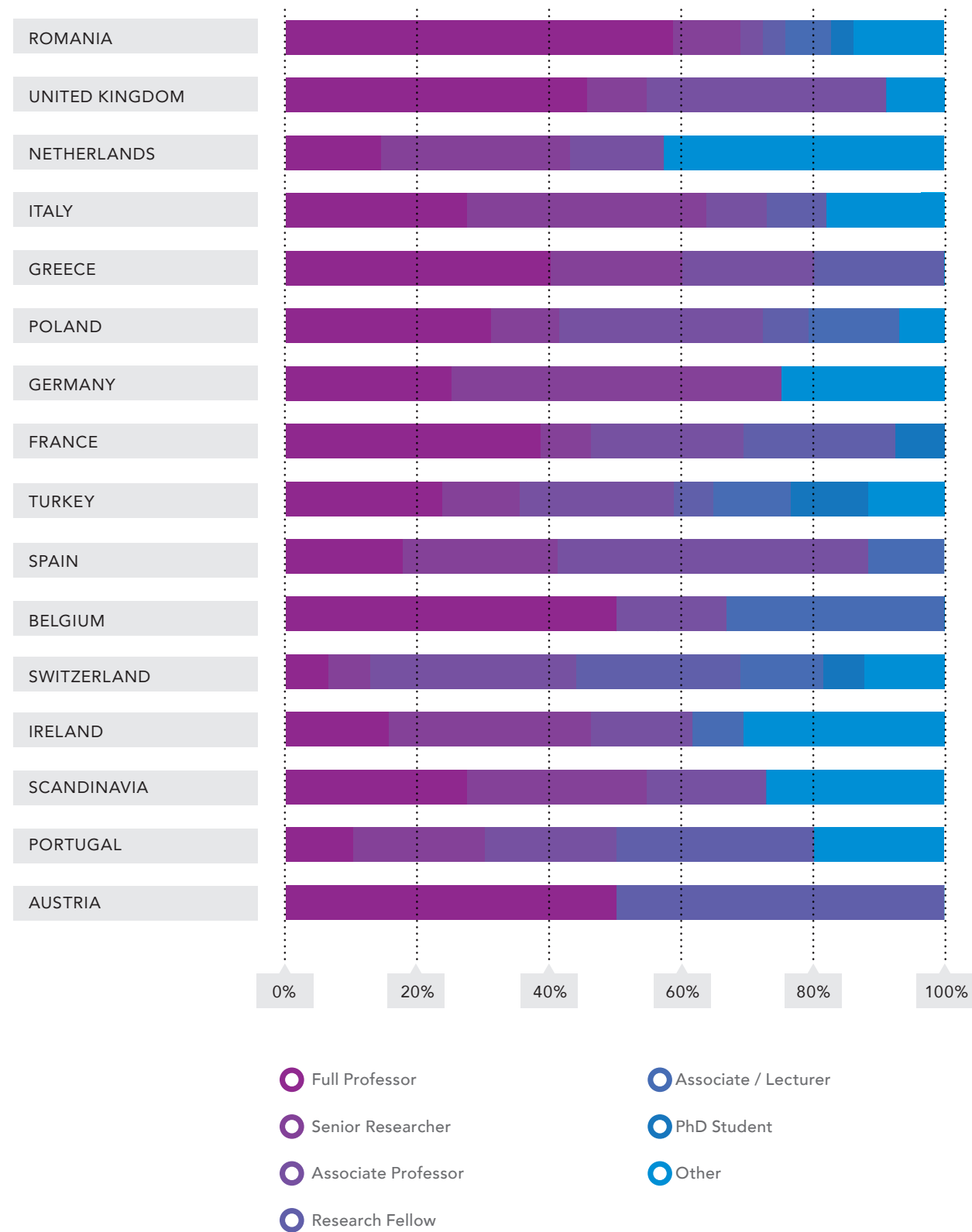
Figure 9.
Years of experience — all countries

The 11-20 years of experience group holds the majority in Romania, Italy, Turkey, Belgium, Germany, Switzerland, Spain. The 21-30 years group is the largest in UK, France and Ireland. Countries where more junior profiles (0-10 years) have the majority are Greece, The Netherlands and Poland.

Figure 9 — Years of experience bar chart.

Y-axis: 0, 10, 20, 30, 40, 50, 60, 70, 80
X-axis categories: 0-10 YEARS, 11-20 YEARS, 21-30 YEARS, 30+ YEARS
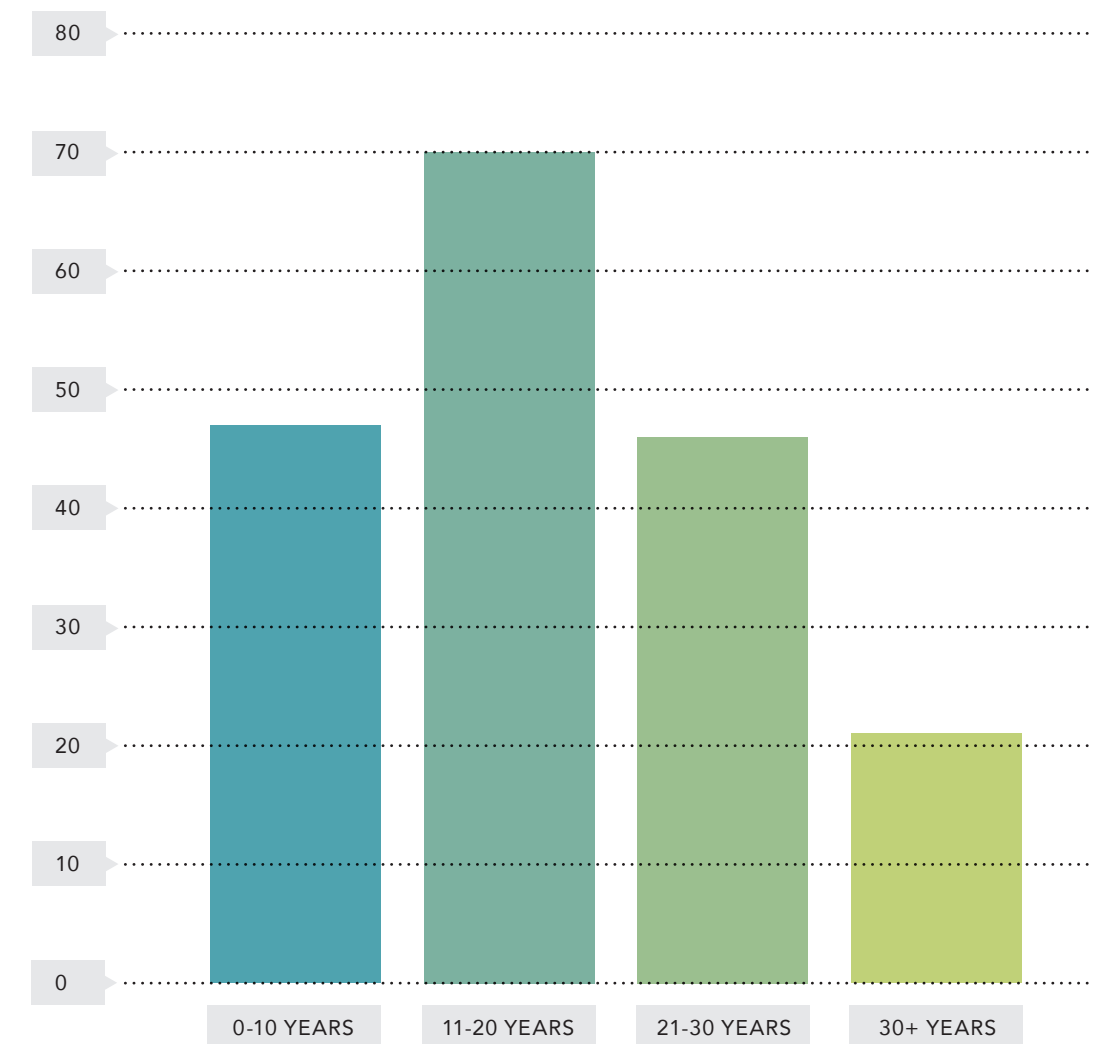
Figure 10.
Years of experience — by country

The 11-20 years of experience group holds the majority in Romania, Italy, Turkey, Belgium, Germany, Switzerland, Spain. The 21-30 years group is the largest in UK, France and Ireland. Countries where more junior profiles (0-10 years) have the majority are Greece, The Netherlands and Poland.
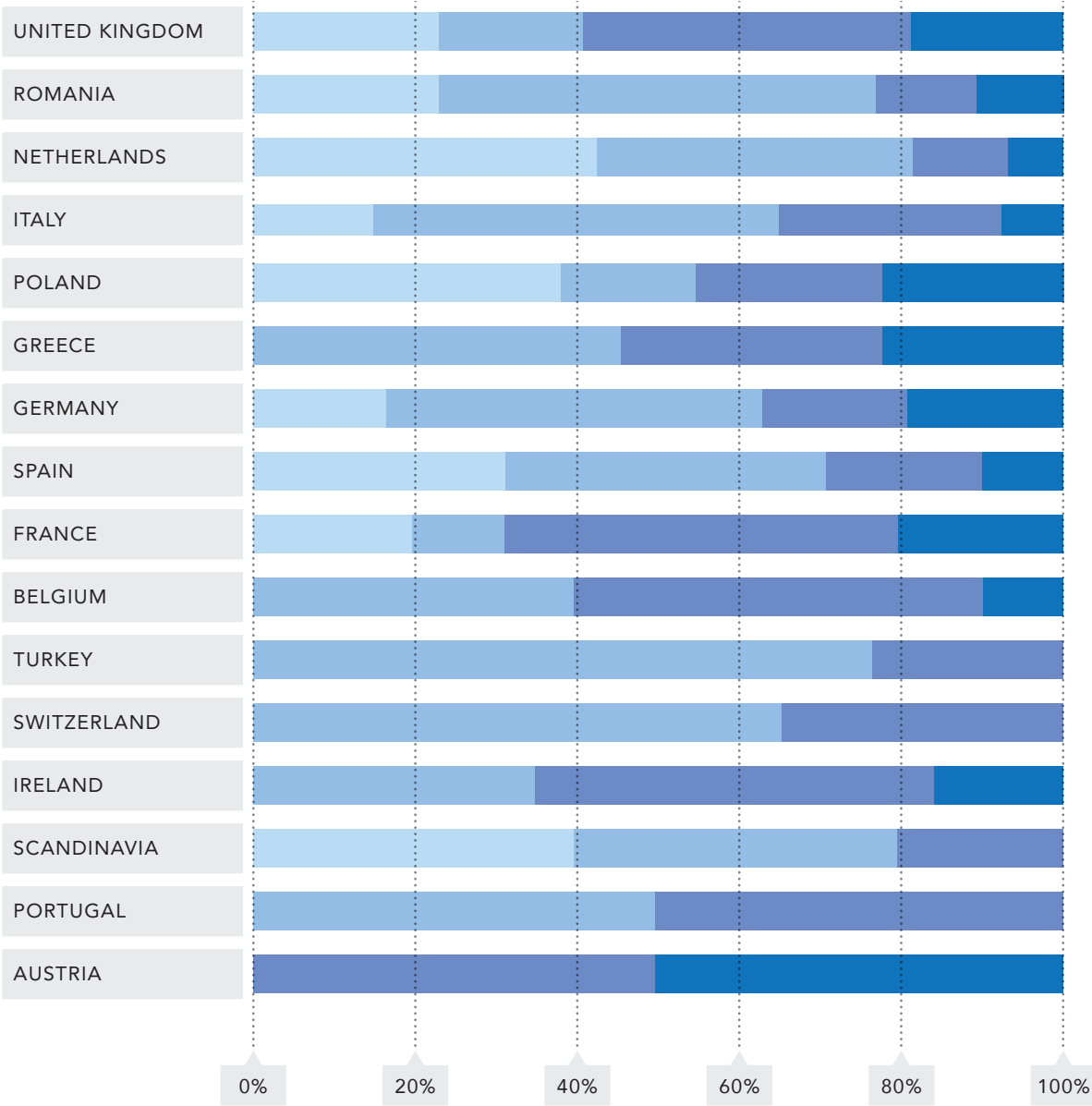
NB: 18 respondents did not fill this information.

- 0-10 years
- 11-20 years
- 21-30 years
- more than 30 years

2.3. Work content

Respondents were asked to specify the main tasks involved in their job, specifically to pick up to a maximum of 5 (out of 8 items as depicted in Table 3 below). Each cell in Table 3 contains the percentage of co-occurrences between each pair of items. Frequency pairs are colour-coded from highest (red) to lowest (white) levels. The core of work activities among respondents encompass traditional categories of research such as:

- "Preparing research proposals" and "Writing scientific articles" (15%)
- "Laboratory work" and "Writing scientific articles (13%)
- "Preparing research proposals" and "Laboratory work" (12%)

Other types of activities such as "Engaging with stakeholders", "IP protection strategy" and "Planning strategy" exhibit intermediate levels of frequency especially when in combination with core job tasks such as "Preparing research proposals" and "Writing scientific articles".
"Ensuring compliance for accreditation of facilities" is the category with the lowest mean relative frequency.

Table 3.
Job Task combinations

	a	b	c	d	e	f	g	h
a. Engage with stakeholders		0.35 %	2.79 %	3.22 %	2.52 %	1.22 %	5.66 %	5.48 %
b. Ensuring compliance for accreditation of specialised facilities			0.52 %	0.78 %	0.52 %	0.52 %	0.96 %	0.96 %
c. IP Protection Strategy (e.g. Patents)				2.87 %	2.18 %	1.04 %	5.05 %	4.79 %
d. Laboratory work					2.87 %	1.48 %	11.58 %	12.62 %
e. Planning strategy (e.g. Business Plan, Marketing)						1.22 %	4.61 %	4.44 %
f. Preparing legal or regulatory documents							2.44 %	2.26 %
g. Preparing research proposals								15.06 %
h. Writing scientific articles								

Figure 11.
Job Task combinations

IP PROTECTION STRATEGY
(E.G. PATENTS)

PREPARING LEGAL OR
REGULATORY DOCUMENTS

WRITING SCIENTIFIC
ARTICLES

ENGAGE WITH
STAKEHOLDERS

ENSURING COMPLIANCE
FOR ACCREDITATION OF
SPECIALISED FACILITIES

PREPARING RESEARCH
PROPOSALS

LABORATORY
WORK

PLANNING STRATEGIES
(E.G. BUSINESS PLAN, MARKETING)

- Analytical exploratory
- Processing information
- Information
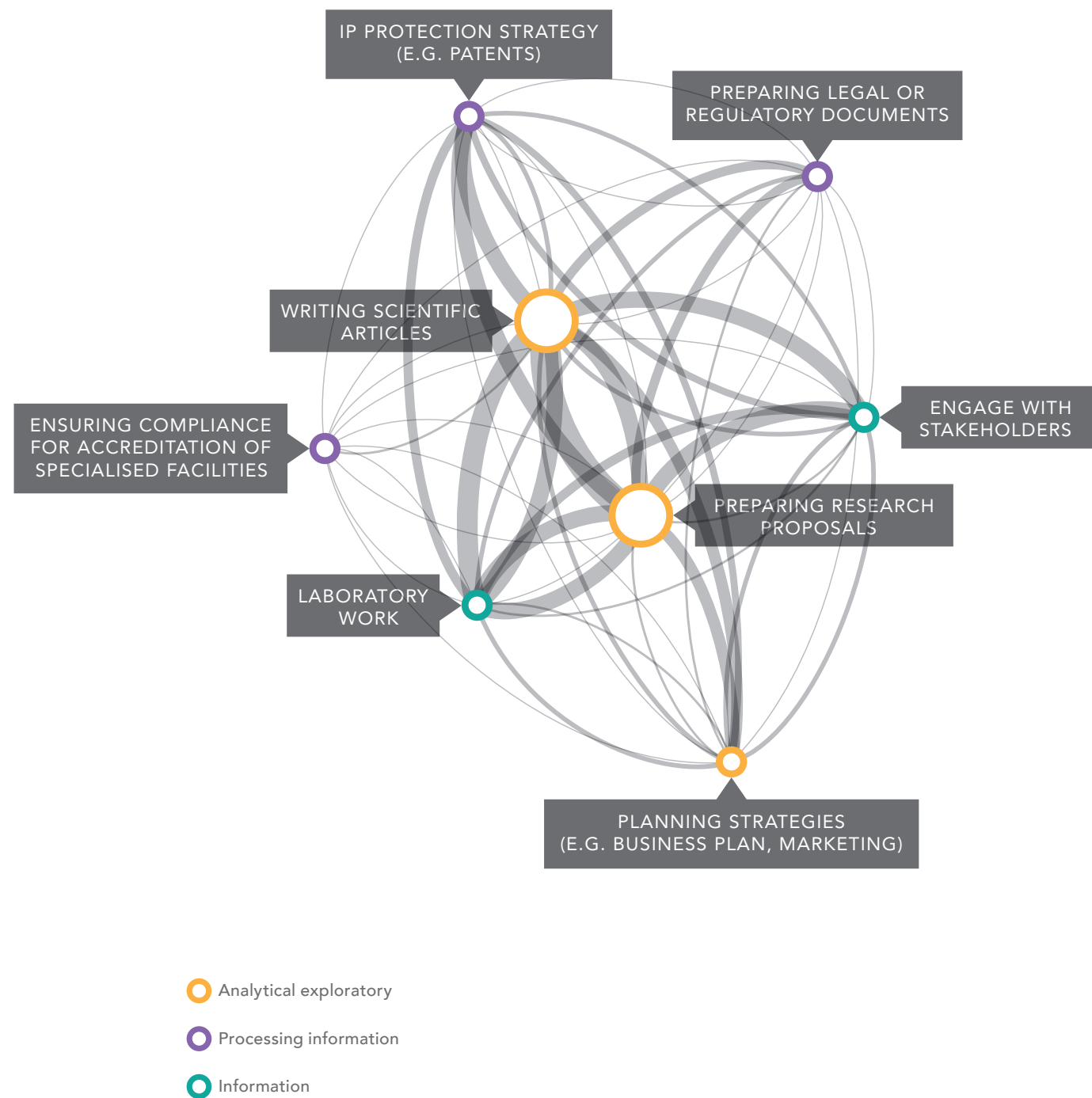
Figure 12.
Technical Equipment

Respondents were asked to indicate
the type of equipment available in
the research facilities in which they
are employed.

Aggregation by European macro-
regions and by type of equipment
indicates that while the combination
"In Vivo experimentation"-"Sensors,
Micro and Nanodevices" has the
largest share in Southern and
Central Europe, "Computing and in-
silico modelling" exhibits a stronger
presence in Northern and Eastern
Europe.

SOUTHERN EUROPE

NORTHERN EUROPE

EASTERN EUROPE

CENTRAL EUROPE

0%   20%   40%   60%   80%   100%

- Tissue engineering constructs and testing
- Sensors, micro and nanodevices
- Physico-chemical characterisation of biomaterials
- In vivo experimentation
- In vitro cell and molecular biology
- Imaging
- Computing and in silico modelling
- Biomaterials characterisation
- Biomaterial synthesis and engineering

2.4. Funding

General public funding appears to be the main source of funding in almost 50% of all responses. The other half of funding comes from Fellowships (e.g. ERC Grants) (17%), Industry (16%) and Public/Private Partnerships (11%).

Figure 13. Sources of funding — all countries

The patterns by country reflect by and large the aggregate figures, with public funding holding the lion share in almost all countries. Portugal and the Netherlands are the exception, with the lowest shares of public funding (20%) and by contrast the highest shares of Fellowships (46% and 39% respectively) together with Belgium (46%). Public Private Partnerships have the relative highest frequency in Italy (34%) while Industry plays a stronger role in UK, Ireland and Spain.

- General public funding
- Priority driven
- Public / Private partnerships
- Industry
- Charity
- Fellowships (e.g. ERC Grants)
- Other
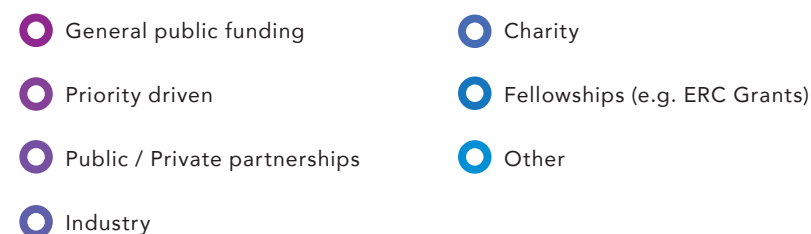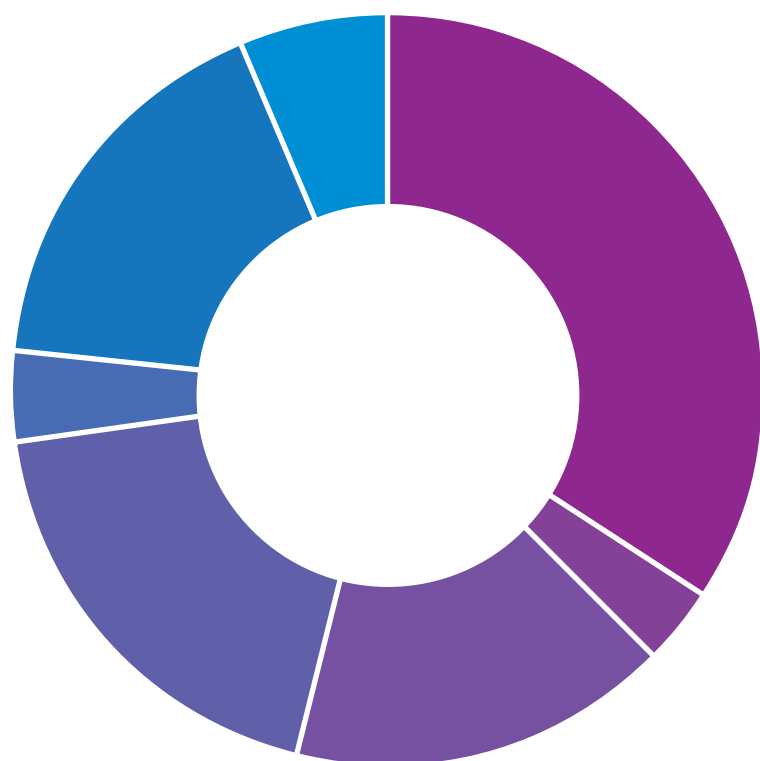
Figure 14. Source of funding — by country

- General public funding
- Priority driven
- Public / Private partnerships
- Industry
- Charity
- Fellowships (e.g. ERC Grants)
- Other

Table 4.
Research output

Respondents were asked to indicate the main outputs of their research activity (over the last 3 years), reporting the specific number of instances in which they have obtained each of the 11 output-related items listed in Table 4.

Table 4 below displays the proportion of respondents, by macro-Region, who experienced at least once any of the 11 output-items. For instance, the first column reports figures for "Products on the market" achieved as an output from the research activities conducted by respondents over the last three years. Table 4 shows that, on average, 15.4% of respondents indicated that they have experienced this output at least once, with minor variations for respondents across the four macro European regions considered. As expected, 'Scientific Publications' are the most frequent outputs obtained by respondents (above 90% of respondents obtain at least 1 publication over the last three years). In contrast, the outputs associated with commercialization achievements are the least frequent. These items include: 'Products on the market', 'Creation of new companies & start-ups' and 'Technology Licenses', which display a comparatively low proportion of respondents (15.4%, 19.9% and 18.4%, respectively).

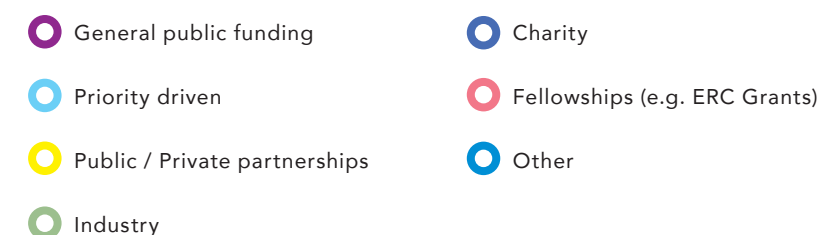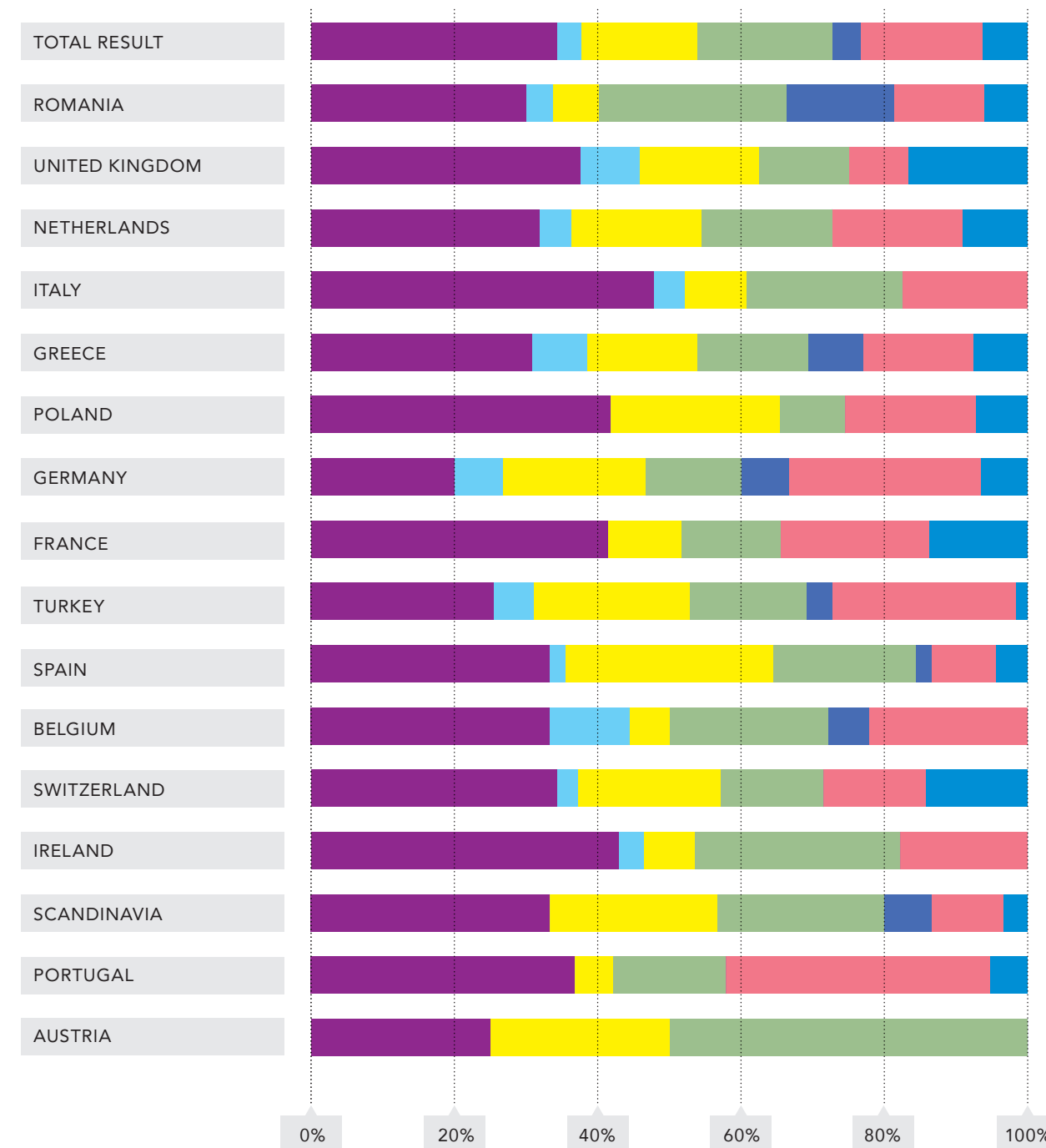| Macro-Regions	Central Europe	Eastern Europe	Northern Europe	Southern Europe	Total
Products on the market	11.3%	15.1%	21.3%	14.5%	15.4%
Product in clinical trials	24.5%	28.3%	27.7%	22.9%	25.9%
Patent applications	66.0%	50.9%	74.5%	54.2%	61.2%
Approved patents	37.3%	34.0%	55.3%	41.7%	41.8%
Creation of new companies & start-ups	18.9%	9.4%	34.0%	18.8%	19.9%
Collaboration agreements with SMEs and large companies	71.7%	47.2%	72.3%	60.4%	62.7%
Scientific publications	90.6%	98.1%	91.5%	93.8%	93.5%
Technology licenses	15.1%	18.9%	27.7%	12.5%	18.4%
Technological publications	24.5%	43.4%	35.0%	18.8%	30.4%
Collaboration agreements with patient/public interest group	16.9%	24.5%	25.5%	25.0%	22.9%
Collaboration agreements with non-profit organisations	30.2%	26.4%	29.8%	22.9%	27.4%

3. Research Projects

This part of the report focuses on project-level information as reported by individual respondents. Before delving into the results, let us concisely sum up the goals and the significance of this exercise.

3.1.
Collaboration and networks in the literature

Initiatives to encourage cooperation between multiple communities like academic scientists and hospitals practitioners have become central ingredients in the policy agenda to enhance innovation in health. A manifestation of this is the widespread adoption of the 'translational research' initiatives, advocating research pathways that connect "the bench and the bedside" (Drolet & Lorenzi, 2011), and which have permeated the policy agenda of the majority of public and private funding agencies worldwide.

Knowledge creation and exchange in the biomedical context are particularly challenging since they involve communication and interaction between different professional groups. Evidence suggests the presence of strong social boundaries between multiple professional communities that differ in terms of professional roles, identities and traditional work practices. (Ferlie, Fitzgerald, Wood, & Hawkins, 2005; Gittelman, 2013). Therefore, a major challenge for translational research is not only to bring together contrasting scientific paradigms (i.e. basic versus applied logics) but also to facilitate the effective flow of knowledge between these communities.

A growing body of literature frames the question of coordination across different communities in the context of network configurations. In particular, scholar in management and social studies on technology relies on network approaches to examine whether certain arrangements concerning the connection among individuals can explain empirical regularities in terms of particular outcomes. This has been the case in studies on job performance (Sparrowe, Liden, Wayne, & Kraimer, 2001), innovation (Obstfeld, 2005; Wu et al., 2008) or creativity in organizations (Baer, 2010; Burt, 2004; Perry-Smith, 2006).

However widespread, the use of network approaches for the study of scientific collaboration remains widely debated, and differing views can lead to very diverse interpretations.

Some scholars argue that dense personal networks, whereby the contacts of a focal actor are highly connected to each other, are more effective for promoting trustful relationships. In these contexts, fast moving information and reliable communication channels facilitate the exchange of sensitive information thus leading to successful complex problem-solving (Fleming, Mingo, & Chen, 2007; Powell, Koput, & Smith-Doerr, 1996; Reagans & McEvily, 2003; Uzzi, 1997). The downside is that dense networks may lead to the formation of redundant ties, as contacts may provide similar information to the focal actor (Coleman, 1988; Uzzi, 1997).

A contrasting view argues in favor of sparse personal networks characterized by few connections between members. This type of configuration grants focal actors privileged access to information that is diverse by virtue of the missing connection between the alters and entails therefore higher exposure to diverse perspectives and ideas (Burt, 1995, 2004; Fleming

et al., 2007). Such a structure tends to be rather common in communities of science that deal with extremely complex problems as once existing options have reached a plateau of effectiveness, actors will naturally tend to look outside of their comfort zone to reframe their research problems.

While sparse collaborative networks potentially increase the pool of available know-how, focal actors embedded in extreme sparse personal networks may experience difficulties in accessing, or even identifying, useful resources due to lack of mutual trust and of weak expectation about the credibility of partners (Schilling & Phelps, 2007). Thus, the tension between sparse and dense network structures is a key issue for understanding the likelihood that particular collaborative arrangements yield successful outcomes. These issues are analysed in the remainder of the report with a view to identify whether and to what extent particular network configurations are associated with translational outcomes.

3.2. ESB networks

The questionnaire asked respondents to report about the research projects in which they have been involved over the previous 3 years. Respondents were invited to select up to a maximum of three types of projects corresponding to the following 9 categories: Drug delivery; Medical Device; Cell-based Therapy; Gene-based Therapy; Tissue Engineering; Biomaterials for Regenerative Medicine; Implants; Diagnostics related to Biomaterials; Other type of projects.

According to their responses, 39 out of the 201 respondents (i.e. 19%) selected a single project type, 38 selected two types of projects (19%), and 124 selected three types of projects (62% of respondents). On average, respondents selected about 2 types of projects and, overall, the data collected in this part of the survey corresponds to a total of 487 project-level data points.

About 70% of the 201 respondents worked on projects in Biomaterials for Regenerative Medicine. The second most frequent projects correspond to the research area of Tissue Engineering: 43% of respondents worked on these projects, and projects in Tissue Engineering represent 18% of the 487 project-level data. The third most frequent type of projects correspond to Implants: 37% of respondents worked on Implant-related projects, and these projects represent 15% of the 487 project-level data.

Figure 15. Project type corresponding to the 487 project–level data – All countries

The predominance of projects in Biomaterials for Regenerative Medicine is visible in the majority of countries. The main exception is the Netherlands, which has a more balance portfolio across categories, while Tissue Engineering has a higher share in Portugal, Turkey and Spain. Projects on Implants are more frequent in France, Poland and Ireland. Italy displays a comparatively greater degree of specialization in Drug Delivery together with Switzerland and, to a lesser degree, Portugal and the UK.

- Biomaterials for regenerative medicine
- Tissue engineering
- Implants
- Medical device
- Drug delivery
- Cell based therapy
- Other type of project
- Diagnostics related to Biomaterials
- Gene based therapy

Figure 16. Project type
– by country

Figure 16. Project type – by country

Legend:
- Biomaterials for regenerative medicine
- Cell based therapy
- Diagnostics related to Biomaterials
- Drug delivery
- Gene based therapy
- Implants
- Medical device
- Tissue engineering
- Other type of project

Countries (top to bottom): ROMANIA, UNITED KINGDOM, NETHERLANDS, ITALY, GREECE, POLAND, GERMANY, FRANCE, TURKEY, SPAIN, BELGIUM, SWITZERLAND, IRELAND, SCANDINAVIA, PORTUGAL, AUSTRIA

3.3. Project–level outputs

Respondents were asked to indicate the main output of the projects in which they have been involved. A list of 7 different types of outputs was provided, and respondents were asked to select as many of the items as applied to the particular research project. The list of output-related items included: (1) Clinical Trials; (2) New patent applications; (3) Creation of a new company / start-up; and (4) Patent / technology license; among other outputs such as scientific publications and publications on technology-oriented journals.

Responses were grouped by levels of 'translational capacity' of the attendant output, indicating the extent to which the outputs reflect more early phases of translational capacity (invention - THINK), more intermediate phases (product development - SEARCH) or more close-to-market phases (commercialization – DO). According to this criteria, we included responses to "New patent applications" as suggesting early phase of translational outputs (i.e. Think); responses to "Clinical Trials" as capturing intermediate translational outputs (i.e. Search), and we created a measured for "Commercialisation" (i.e. Do), which includes two types of outputs: (i) creation of a new company / start-up and (ii) Patent / technology license.

Cells in Table 5 contain the percentage of respondents who indicated whether the projects they contributed to entailed any of the outputs in the columns.

- For the overall range of 478 projects, we observe that 41.5% of them have been associated with the achievement of Patent Applications, 35.3% with the achievement of Commercialization outputs, and 20.5% with the participation in Clinical Trials.

- Patent Applications are particularly frequent for projects in Medical Devices, Implants, Biomaterials for Regenerative Medicine, Diagnostics related to Biomaterials and Drug Delivery.
- Clinical Trials exhibit higher co-occurrences with Medical Devices, Implants and Cell-based Therapy.
- Commercialisation activities tend to spread rather evenly across all project activities with higher concentration in projects that involve Medical Devices, Drug Delivery and Biomaterials for Regenerative Medicine.
- Gene Based therapy and Tissue Engineering are the types of projects with the lowest co-occurrences.

Table 5. Types of outputs per project categories

Project Categories	THINK e.g. planning activities, basic research Patent Applications * Yes	No	SEARCH e.g. testing activities, applied research Clinical trials * Yes	No	DO e.g. tangible outputs closer to clinical applications Commercialisation Yes	No	N. Obs.
Biomaterials for Regenerative Medicine	42,10%	57,90%	12,90%	87,10%	36,40%	63,60%	140
Tissue Engineering	29,90%	70,10%	12,60%	87,40%	31,00%	69,00%	87
Implants	48,00%	52,00%	36,00%	64,00%	33,30%	66,70%	75
Medical Device	63,20%	36,80%	38,60%	61,40%	49,10%	50,90%	57
Drug Delivery	40,00%	60,00%	10,00%	90,00%	38,00%	62,00%	50
Cell Based Therapy	35,70%	64,30%	35,70%	64,30%	35,70%	64,30%	28
Diagnostics related to Biomaterials	42,10%	57,90%	26,30%	73,70%	21,10%	78,90%	19
Gene Based Therapy	25,00%	75,00%	0,00%	100,00%	25,00%	75,00%	8
Other Projects	21,70%	78,30%	8,70%	91,30%	26,10%	73,90%	23
Total (all projects)	41,50%	58,50%	20,50%	79,50%	35,30%	64,70%	487

3.4. Barriers

Respondents were asked to indicate the main barriers that were encountered in each of the research projects to which they participated. Cells contain the percentage of respondents who indicated any type of barrier as either "important" or "very important" in terms of hampering project achievements. Results are broken down by project type.

Budget constraints stand out by a margin over all other categories: overall, respondents in 77.8% of the 487 projects reported ´budget constraints´ as either being important or very important. In about 43% of the projects, respondents reported significant barriers with regards to ´Regulation´ associated with new product and services. Lacking facilities and missing expertise were comparatively of lower importance as factors hampering research projects.

Table 6. Importance of barriers per project type

Project type	Budget contraints	Lacking facilities	Missing expertise	Product / Service Regulation
Biomaterials for regenerative medicine	78,0%	38,0%	24,0%	48,0%
Cell based therapy	75,4%	38,6%	31,6%	49,1%
Diagnostics related to Biomaterials	78,6%	32,1%	35,7%	53,6%
Drug delivery	87,5%	37,5%	12,5%	37,5%
Gene based therapy	81,6%	39,1%	27,6%	46,0%
Implants	77,1%	40,0%	24,3%	36,4%
Medical device	80,0%	45,3%	26,7%	42,7%
Tissue engineering	73,7%	31,6%	21,1%	47,4%
Other type of Project	65,2%	47,8%	30,4%	30,4%
Total (all projects)	77.8%	39.8%	26.7%	42.91%

3.5. Patterns of collaboration: diversity of project partners

Respondents were asked to indicate the type of research partners they collaborated with in each of the research projects to which respondents participated. The questionnaire included 10 broad categories of possible partners, including: (1) basic scientists, (2) applied scientists, (3) clinical scientists, (4) biomaterials suppliers, (5) medical device manufacturers, (6) pharma companies, (7) contract companies, (8) medical practitioners, (9) representatives of patient groups, and (10) regulatory bodies and national health agencies. Moreover, for each of the company-type of partners, the questionnaire specified whether partners corresponded to any of the following categories: managers, researchers or technicians. For Medical practitioners, the questionnaire specified whether partners refer to: nurses, physicians or technicians. Finally, for Regulatory Bodies the questionnaire distinguished whether partners were: executives or professionals (e.g. lawyers, engineers, etc). To simplify the reporting of this information, Table 7 reports information on the 10 broad categories of research partners.

Cells in Table 7 contain the percentage of respondents who indicated whether the projects they contributed to entailed collaboration with any of the partner types in the columns.

- Basic Scientists and Applied Scientists participate in above 70% of the reported projects. However, it is worth noting that there are significant differences in the extent to which these types of partners participate in research projects, when comparing different project categories. For instance, basic scientists are comparatively less likely to participate in projects associated with Medical Devices than in projects associated with Tissue Engineering or Drug Delivery.

- The involvement of Patient Groups, Regulatory organizations and Pharma Companies is among the lowest. Again, we observe significant statistical differences across project categories. For instance, the involvement of Patients Groups in research projects is much more frequent in Cell-based Therapy and Diagnostic related to Biomaterials, compared to most other project categories.

Table 7.
Patterns of collaboration

Project Categories	Basic Scient.	Applied Scient.	Clinical Scient.	Biomaterial Suppliers	Contract Firms	Medical Device Manuf.	Medical Pract.	Regulatory Organisat.	Patient Groups	Pharma Firms	N. Obs
Biomaterials for Regenerative Medicine	80.00%	73.60%	47.90%	46.60%	17.90%	29.30%	36.40%	10.00%	2.90%	9.30%	140
Tissue Engineering	85.00%	80.50%	39.10%	50.60%	14.90%	18.40%	27.60%	5.80%	0.00%	2.30%	87
Implants	61.30%	73.30%	46.70%	40.00%	13.30%	40.00%	37.30%	12.00%	1.30%	2.70%	75
Medical Device	52.60%	64.90%	28.10%	24.60%	21.10%	54.40%	36.80%	14.00%	1.80%	10.50%	57
Drug Delivery	88.00%	56.00%	46.00%	28.00%	14.00%	20.00%	12.00%	4.00%	0.00%	32.00%	50
Cell Based Therapy	82.10%	60.70%	67.90%	32.10%	18.90%	10.70%	39.30%	10.70%	7.10%	10.70%	28
Diagnostics related to Biomaterials	73.60%	84.20%	57.90%	31.60%	15.80%	26.30%	26.30%	15.80%	5.30%	10.50%	19
Gene Based Therapy	100.00%	87.50%	37.50%	12.50%	12.50%	0.00%	0.00%	0.00%	0.00%	37.50%	8
Other Type of Projects	78.20%	60.90%	34.80%	30.40%	13.00%	21.70%	8.70%	17.40%	4.40%	4.40%	23
Total (all projects)	75.80%	71.30%	44.40%	39.00%	16.20%	28.90%	30.40%	9.90%	2.10%	9.90%	487

3.6. Patterns of collaborations: network density

The questionnaire asked respondents to report whether, according to the best of their knowledge, the nominated partners participated in other research projects in which the respondent was not involved. This information allowed us to assess the density of the research network associated to each single project. The density of a network is the ratio between the number of links between the collaborators and the maximum number of possible links, and for this reason, the density scores range between 0 and 1. The higher is the value (i.e. the closer to 1), the denser the network. While the lower is the score (the closer to 0), the lower the degree of density of the network. Network density is a property that captures the degree of cohesiveness of the network in the sense that it reflects the degree to which all nominated partners know (in this case, collaborate with) each other.

Table 8 reports a summary of the density scores that correspond to all the projects in our sample (i.e. 478). The most frequent type of project-level collaborative network has 3 partners (71% of projects share this feature) and, among these type of networks, the most typical density scores correspond to the extremes: lowest (score 0) and highest (score 1), each accounting for about 20% of all the project cases. As we can see from the last raw, 25% of projects have an intermediate density score ranging between 0.34 and 0.66.

Table 8.
Network density

Number of partners in a research project	Density scores					Total
	0	0 – 0.33	0.34 – 0.66	0.67 – 0.99	1	
3	20,3%	12,5%	15,6%	0,0%	22,8%	71,3%
4	2,9%	2,1%	3,9%	0,6%	3,5%	12,9%
5	1,4%	1,0%	2,3%	3,3%	1,2%	9,2%
6	0,2%	0,6%	0,8%	0,2%	0,2%	2,1%
7	0,0%	0,4%	1,2%	0,4%	0,2%	2,3%
8	0,0%	0,0%	0,6%	0,2%	0,0%	0,8%
9	0,0%	0,0%	0,2%	0,2%	0,4%	0,8%
10	0,2%	0,0%	0,2%	0,2%	0,0%	0,6%
Total	25,1%	16,6%	24,8%	5,1%	28,3%	100,0%

3.7. Examples of network types

Questionnaire respondents are labeled as "central actors". All other actors correspond to the partners nominated by the central actor.

Figure 17.
3 collaborators low density (density=0)

The network depicted in Figure 17 shows a project-network in which the central actor reported the collaboration with three types of partners, neither of whom have collaborated with each other (according to the information provided by the central actor: i.e. the survey respondent). Therefore, in this case, we have an example of a research network with a density score equal to zero, the lowest density.
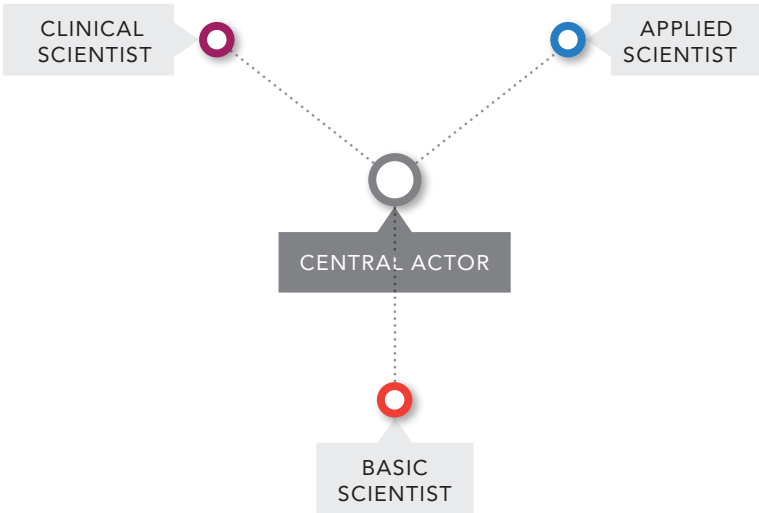
Figure 18.
3 collaborators high density (density=1)

The network depicted in Figure 18 shows a project-related network in which the central actor also

reported the collaboration with three types of partners (same three types as in Figure 17). However, in this case, all project partners have collaborated with each other in research projects which do not involve the central actor. Therefore, in this case, we have an example of a research network with a density score equal to 1, the highest possible density.

Figure 19.
6 collaborators and medium–low level of density (density = 0.27)

The network depicted in Figure 19 shows a project-related network in which the central actor has reported

collaboration with six types of partners (which is a somewhat intermediate level of network diversity, if we consider the 10 broad types of categories included in the questionnaire (and specified above with regards to Table 7). Moreover, in this example, several project partners have collaborated with each other in research projects which do not involve the central actor, and thus, we have a research network with an intermediate level of density (a intermediate-low score of 0.27).

Figure 20.
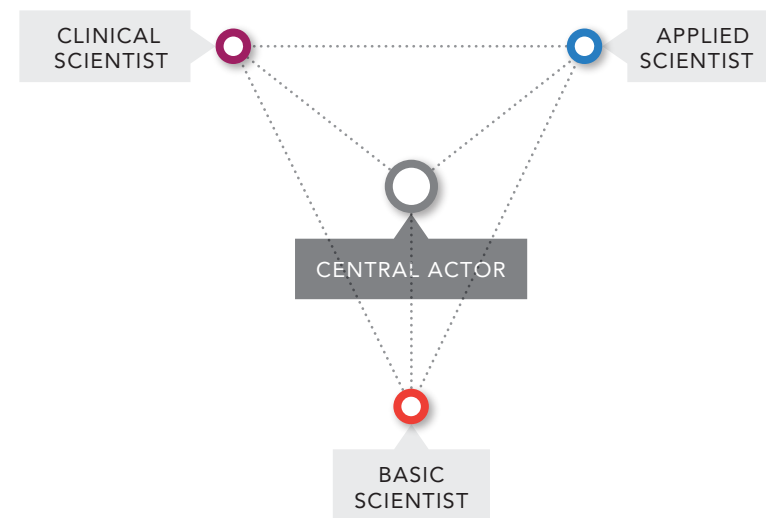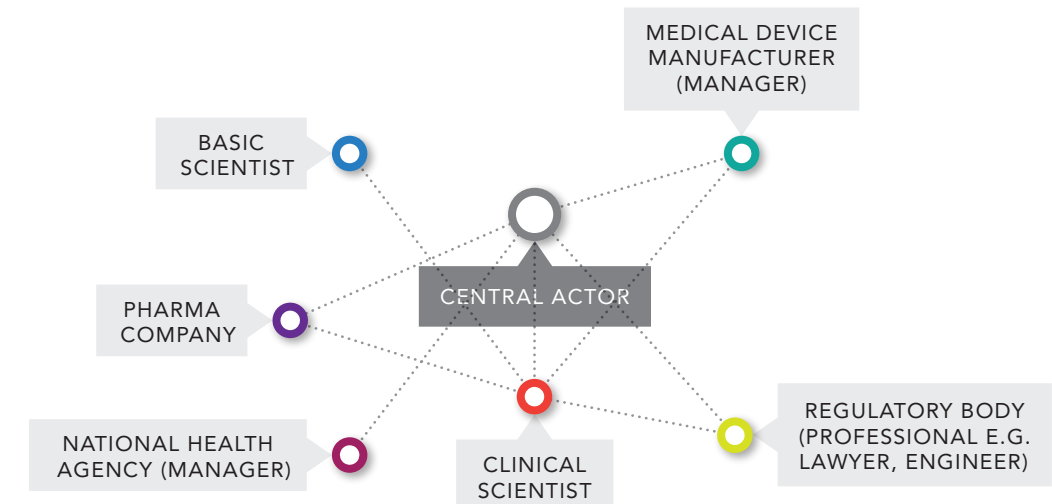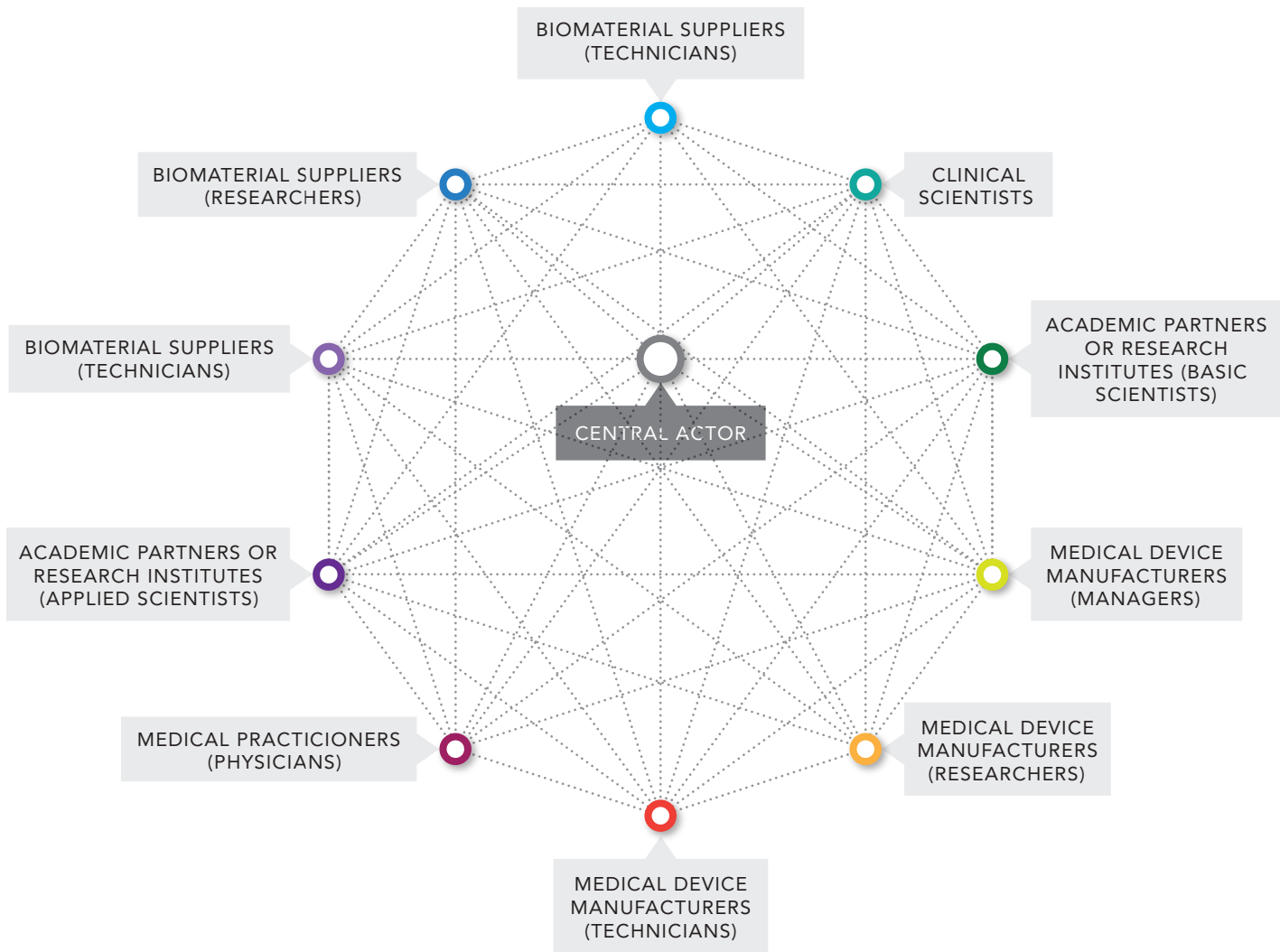### 10 collaborators and high level of density (density = 0.98)

Finally, the network depicted in Figure 20 shows a project-related network in which the central actor has reported collaboration with 10 types of partners. In this case, this network involves partners who correspond to a similar broad category, such as in the case of Biomaterials suppliers, including managers, researchers and technicians (of Biomaterial supplier companies). This implies a high level of network diversity. Moreover, in this example, almost all project partners have collaborated with each other in research projects which do not involve the central actor, and thus, we have a research network with an extremely high level of density (a density score close to one: 0.98).

BIOMATERIAL SUPPLIERS (TECHNICIANS)

BIOMATERIAL SUPPLIERS (RESEARCHERS)

CLINICAL SCIENTISTS

BIOMATERIAL SUPPLIERS (TECHNICIANS)

CENTRAL ACTOR

ACADEMIC PARTNERS OR RESEARCH INSTITUTES (BASIC SCIENTISTS)

ACADEMIC PARTNERS OR RESEARCH INSTITUTES (APPLIED SCIENTISTS)

MEDICAL DEVICE MANUFACTURERS (MANAGERS)

MEDICAL PRACTICIONERS (PHYSICIANS)

MEDICAL DEVICE MANUFACTURERS (RESEARCHERS)

MEDICAL DEVICE MANUFACTURERS (TECHNICIANS)

3.8.
Relationship between Network Diversity/ Network Density and Translational Outputs

The fundamental variables used in our analysis are listed in Table 9.

Table 9.
Descriptive statistics

Since the three dependent variables are not independent events (meaning that the occurrence of one type of translational output tends to be associated with the generation of another translational output in a research project), we use Mutlti-variate probit regression models. This multivariate method allows us to estimate the factors that are significantly associated with the probability of obtaining a particular translational output from a research project.

Name	Mean	Stand. Dev.	Min.	Max.	N
Patent Applications (y/n)	0.415	0.493	0	1	487
Clinical Trials (y/n)	0.205	0.404	0	1	487
Commercialisation (y/n)	0.353	0.478	0	1	487
Network Diversity	3.277	1.030	1	8	487
Network Density	0.527	0.386	0	1	487
Medical Practitioners & Patients (y/n)	0.306	0.461	0	1	487
Multi_Tasking	3.862	1.056	1	5	487
PhD Age (years since awarded PhD)	15.140	9.623	0	40	487
Professor (y/n)	0.230	0.459	0	1	487
Scientific Publications*	17.739	24.029	0	200	487
Technological Publications*	1.647	4.743	0	50	487
Hospital_University (y/n)	0.238	0.426	0	1	487
Eastern Europe (y/n)	0.251	0.434	0	1	487
Northern Europe (y/n)	0.248	0.433	0	1	487
Southern Europe (y/n)	0.246	0.431	0	1	487

* The figures for these variables display the raw values rather than the logarithmically transformed ones that we use in the econo-metric analysis.
(y/n) refer to dichot-omous variables (i.e. take values 1 or 0). All other variables are either continuous or categorical.

Table 10.

Results of Multivariate probic regressions: Dependent variables: Patents Applications / Clinical Trials / Commercialisation (Dichotomous variables) (N = 478)

The results are presented in two Tables. Table 10 investigates the relationship between the translational outputs and our two main measures capturing the configuration of the network: diversity and density (Model 1). This Table also introduces the estimates for the interplay between density and diversity of networks on the probability of translational outputs in these research projects (Model 2).

	(Model 1)			(Model 2)		
	Patent Applications	Clinical Trials	Commercialisation	Patent Applications	Clinical Trials	Commercialisation
Network Diversity	0.231***	0.262***	0.081	0.049	-0.019	-0.190
	[0.075]	[0.077]	[0.069]	[0.116]	[0.138]	[0.126]
Network Density	-0.410**	-0.161	-0.317	-1.525**	-1.941**	-2.019***
	[0.194]	[0250]	[0.214]	[0.624]	[0.819]	[0.705]
Diversity x Density	---	---	---	0.354*	0.552**	0.539***
				[0.193]	[0.232]	[0.203]
Multi_Tasking	0.254***	-0.116	0.318***	0.257***	-0.122	0.329***
	[0.089]	[0.099]	[0.089]	[0.090]	[0.101]	[0.090]
PhD_Age	0.009	-0.005	0.003	0.010	-0.003	0.005
	[0.010]	[0.011]	[0.009]	[0.010]	[0.011]	[0.009]
Professor	0.347*	0.492**	0.514**	0.352*	0.496**	0.527**
	[0.206]	[0.039]	[0.206]	[0.206]	[0.240]	[0.211]
Scientific Publications (ln)	-0.006	-0.099	-0.042	-0.008	-0.103	-0.047
	[0.086]	[0.090]	[0.084]	[0.086]	[0.092]	[0.083]
Technology Publications (ln)	-0.058	0.198*	0.044	-0.050	0.222**	0.055
	[0.110]	[0.112]	[0.095]	[0.109]	[0.113]	[0.096]
Hospital_University	-0.114	-0.172	-0.539*	-0.147	-0.216	-0.603**
	[0.251]	[0.298]	[0.299]	[0.251]	[0.302]	[0.300]
University	-0.515**	-1.086***	-0.428*	-0.518**	-1.107***	-0.437*
	[0.221]	[0.279]	[0.227]	[0.221]	[0.279]	[0.228]
Eastern Europe	0.203	0.107	-0.108	0.206	0.126	-0.097
	[0.235]	[0.244]	[0.231]	[0.233]	[0.247]	[0.228]
Northern Europe	0.570**	0.369	0.353	0.592**	0.414	0.392*
	[0.243]	[0.275]	[0.231]	[0.243]	[0.276]	[0.232]
Southern Europe	0.033	0.241	-0.179	0.041	0.258	-0.166
	[0.241]	[0.284]	[0.232]	[0.242]	[0.283]	[0.228]
Project Type (dummy)	Included	Included	Included	Included	Included	Included
Log-Likelihood / Wald chi2	Log likelihood = -723.3*** (Wald chi2 (57) = 2405.6)			Log likelihood = -715.9*** (Wald chi2 (60) = 2279.6)		

In the table above, we highlight the estimated coefficients that are statistically significant at the 10% (*), 5% (**) and 1% (***).

Table 11.

Results of Multivariate probic regressions: Dependent variables: Patents Applications / Clinical Trials / Commercialisation (Dichotomous variables) (N = 478)

Table 11 adds a new element into the analysis: to examine whether the inclusion of 'patients and medical practitioners' among network partners exerts a particular influence on the probability to obtain translational outputs (Models 3 and 4).

	(Model 3)			(Model 4)		
	Patent Applications	Clinical Trials	Commercialisation	Patent Applications	Clinical Trials	Commercialisation
Network Diversity	0.169**	0.216***	0.076	0.001	-0.064	-0.192
	[0.080]	[0.082]	[0.074]	[0.117]	[0.143]	[0.130]
Network Density	-0.423**	-0.164	-0.315	-1.471**	-1.936**	-2.015***
	[0.191]	[0250]	[0.214]	[0.620]	[0.832]	[0.704]
Diversity x Density	---	---	---	0.333*	0.550**	0.539***
				[0.191]	[0.238]	[0.203]
Medical Practitioners & Patients	0.429***	0.348**	0.031	0.421***	0.339*	0.013
	[0.159]	[0.176]	[0.187]	[0.158]	[0.178]	[0.180]
Multi_Tasking	0.251***	-0.124	0.317***	0.253***	-0.131	0.327***
	[0.089]	[0.101]	[0.089]	[0.090]	[0.102]	[0.090]
PhD_Age	0.009	-0.005	0.003	0.010	-0.004	0.005
	[0.010]	[0.011]	[0.009]	[0.011]	[0.011]	[0.009]
Professor	0.336*	0.468**	0.514**	0.342*	0.473**	0.528**
	[0.203]	[0.238]	[0.206]	[0.203]	[0.242]	[0.210]
Scientific Publications (ln)	0.009	-0.081	-0.041	0.007	-0.086	-0.047
	[0.083]	[0.090]	[0.083]	[0.083]	[0.091]	[0.083]
Technology Publications (ln)	-0.058	0.204*	0.044	-0.051	0.228**	0.056
	[0.107]	[0.111]	[0.095]	[0.106]	[0.112]	[0.096]
Hospital University	-0.117	-0.163	-0.540*	-0.150	-0.205	-0.604**
	[0.248]	[0.296]	[0.299]	[0.248]	[0.301]	[0.300]
University	-0.548**	-1.107***	-0.430*	-0.551**	-1.128***	-0.438*
	[0.215]	[0.276]	[0.227]	[0.214]	[0.275]	[0.228]
Eastern Europe	0.235	0.132	-0.107	0.238	0.153	-0.098
	[0.228]	[0.247]	[0.230]	[0.227]	[0.250]	[0.227]
Northern Europe	0.575**	0.364	0.352	0.595**	0.407	0.392*
	[0.236]	[0.273]	[0.230]	[0.237]	[0.275]	[0.231]
Southern Europe	0.063	0.252	-0.177	0.068	0.268	-0.166
	[0.235]	[0.286]	[0.233]	[0.236]	[0.285]	[0.232]
Project Type (dummy)	Included	Included	Included	Included	Included	Included
Log-Likelihood / Wald chi2	Log likelihood = -717.2*** (Wald chi2 (60) = 2405.7)			Log likelihood = -710.1*** (Wald chi2 (63) = 2582.3)		

In the table above, we highlight the estimated coefficients that are statistically significant at the 10% (*), 5% (**) and 1% (***).

The main results can be summarised as follows:

- Network Diversity has a positive and significant association with ´patent applications´ and ´clinical trials´, though the relationship is not statistically significant for ´commercialisation´. This means that increasing diversity in the network (as measured by the range of different types of network partners) has a positive influence on the generation of translational outputs (with the exception of 'commercialisation'). These estimates (highlighted in Model 1) are depicted graphically in Figures 17.

- Network Density has overall a negative influence on the three types of outputs, but this relationship is only statistically significant in the case of ´patent applications´. Because of the lack of statistically significance for two out of three output measures, we cannot make a strong statement about the influence of network density on translational outputs. For the case of ´patent applications ´we have depicted the results graphically in Figure 17.

- One of the critical insights from Table 11 is related with the findings about the interplay between diversity and density (see the estimates for the multiplicative term ´Diversity * Density´, highlighted in Model 2). The results show a positive and statistically significant interplay for the three translational outputs examined in this study. These findings provide strong support for the claim about the complementarities between these two elements of the network configuration: diversity and density.

- The interplay between diversity and density is also graphically depicted in Figures 18. These figures reflect the positive interplay between diversity and density on the three translational outputs. In other words, for high levels of network density, we observe a

positive relationship between network diversity and the probability of achieving each of the three translational outputs. While for low levels of density, greater network diversity is likely to be detrimental for the achievement of translational outputs (particularly, in the cases of 'commercialisation' and 'clinical trials'). This means that these two elements of network configuration complement each other: network diversity has a particularly strong effect on the probability of translational outputs when combined with high levels of network density. However, if network density is low, then greater diversity is likely to be detrimental for the generation of translational outputs.

- Finally, Table 11 introduces the dichotomous variable 'Medical Practitioners & Patients', which measures whether the project network includes partners that can be classified as patients, medical practitioners, or both. As highlighted in Models 3 and 4, the estimated coefficients for this variable indicate that including this type of partners in the network is positively and significantly associated with 'patent applications' and 'clinical trials' (while we do not observe a statistically significant association for commercialisation outputs). It is interesting to note that the strongest effect of including patients and medical practitioners in the network is associated with translational outputs at the upstream phase, associated with invention and idea generation (i.e. patent applications), rather than with downstream phases (as captured by commercialisation outputs). This suggests that the information and knowledge obtained from these type of partners may play a more significant role at the idea conception for translational outputs from research activities, as compared to the commercialisation or downstream phases of product development.

Figure 21.
Highlighted estimated coefficients

The three figures below correspond to the three highlighted estimated coefficients in first Table - Model 1.
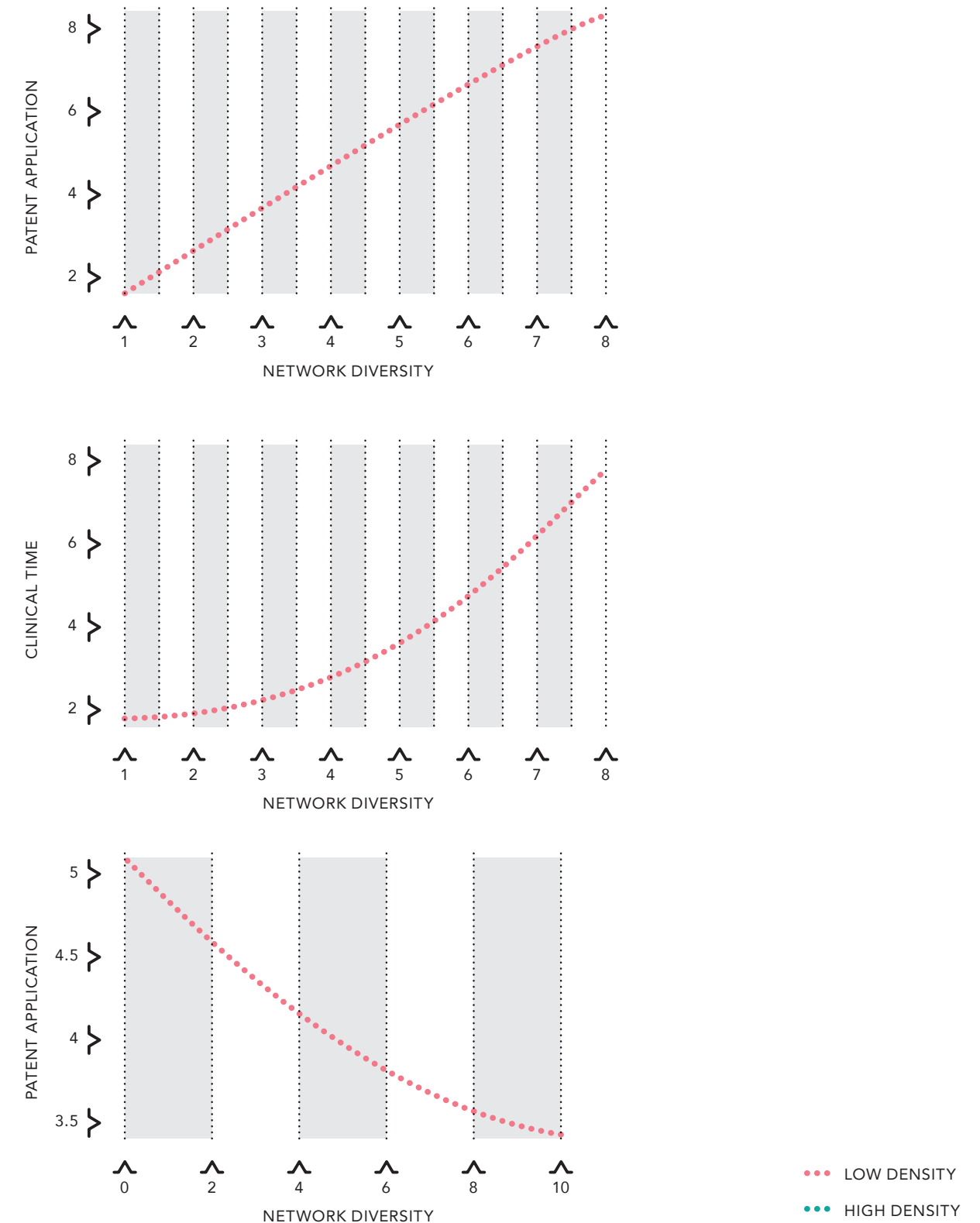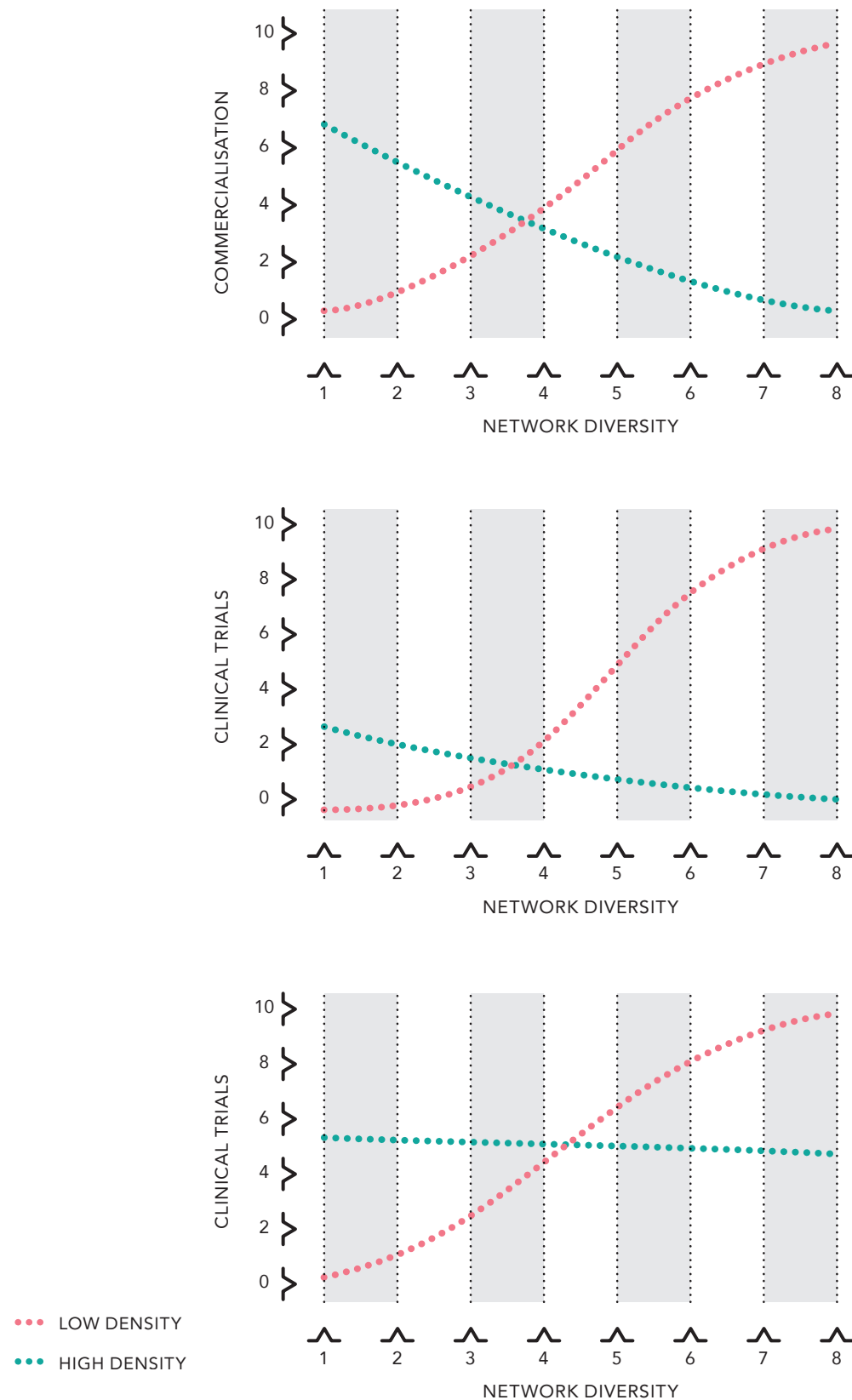

LOW DENSITY
HIGH DENSITY

Figure 22.

Interplay between network diversity and density

COMMERCIALISATION vs **NETWORK DIVERSITY** (1–8), values 0, 2, 4, 6, 8, 10

CLINICAL TRIALS vs **NETWORK DIVERSITY** (1–8), values 0, 2, 4, 6, 8, 10

CLINICAL TRIALS vs **NETWORK DIVERSITY** (1–8), values 0, 2, 4, 6, 8, 10

•••• LOW DENSITY
•••• HIGH DENSITY

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OPINION LEADERS' PAPERS

The Editor's Introduction

Biomaterials :

quo vadis

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On the initiative of the ESB President, Prof. Matteo Santin, with the unanimous agreement of the Council of the ESB, Prof. Maria Dulce Nombre Vallet Regi and I approached several senior members of the Biomaterials Community to solicit their "Opinion" on the future directions of Biomaterials Research.

We are greatful to all those colleagues for their contributions, which follow.

These short papers reveal to the younger generation of Biomaterials Scientists the evolving approaches to dealing with such a complex, highly interdisciplinary scientific subject with the final aim of offering useful therapeutic tools and devices to the 'clinical arsenal'.

As it may be discerned through these Opinion Papers, great advances have already taken place.

And, despite the title of the book that my good friend the late Prof. Jozef Helsen and I published in 2010 " BIOMATERIALS, a Tantalus Experience " , we would like to encourage once again the scientific community to reflect on the following:

'Myths are created by the powerful to intimidate the public even when they are charming. But myths are also useful in driving our thoughts beyond the current horizons of knowledge.'

Stepping gently on the shoulders of the pioneers of this exciting field, new advances are at the horizon to contribute to a healthier life in a better society, with peace reigning everywhere.

Finally, let me say that "words" are useful when are followed by the right "actions".

The biomaterials debate

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A 'leading opinion' should be an authoritative, informed but opinionated, presentation of the status of a subject; it may in part be reminiscent and in part prognostication, but should always be written by someone who has made a contribution to that which is being reminisced about and who also has a stake in that which is prognosticated. Intellectually-informed, but not idly-constructed, controversial statements should add to the value of, and interest in, such a leading opinion. So, what can be said of the status of biomaterials science, a subject which may sound dry and unappealing to the disinterested layman, but which impacts the lives of millions of people, mostly in the rich developed world but increasingly in the poorer emerging and developing world.

There can be no doubt that biomaterials (note that I use the simple noun here and not the compound noun, biomaterials science) have revolutionized areas of medical therapies, transforming or extending the lives of very many patients. This is self-evident from the current-day situation where the sight of millions of people is dependent on the polymers of intraocular lenses, continued heart function in equal numbers is predicated on implanted pacemakers, defibrillators, heart valves and coronary stents, where haemodialysis extends the life of those suffering end stage renal failure, joint replacements allow millions to walk again with freedom from pain, and so on. The reminiscent part of this opinion starts with my early professional life experiences of meeting and talking with some of the pioneers of these clinical technologies, including John Charnley, Willem Kolff, Chris Barnard and Denton Cooley. The overwhelming memories of such meetings were of ambitious, totally driven individuals who, through intuition, conviction and perseverance, visualized and implemented radically new therapies and products. The risks that they took were considerable, and such 'experimental surgery' would not be allowed now; it is quite possible that today's armamentarium of medical devices and procedures would not exist without the benefits of these human experiments. However, although the selection of materials for these products was an important consideration, it was not the most significant, and many pioneers quite simply got the material selection wrong, largely because of a lack of appreciation of the critical balance between functionality and biocompatibility.

The situation has changed somewhat by today, but we have to ask ourselves, how and why. The reason why I stated earlier that it was biomaterials and not biomaterials science that have revolutionized medical therapies, is that biomaterials science still does not properly recognize the criticality of this balance. The problematic use of metal-on-metal hip replacements revealed a poor understanding of the difference between tissue responses to micron-sized polymer wear debris and nano-sized cobalt-chromium wear particles. The reason why polypropylene meshes fail to give 100% satisfaction in urogynaecology applications is related to the poor understanding of the contributions of the biomechanics, sub-clinical infection and the inflammation – fibrosis balance in the female pelvic area. This lack of understanding is now getting in the way of progress in the newer areas of biomaterials applications, including scaffolds (or templates) in tissue engineering and systemically injected nanoparticulate products for diagnostic and therapeutic purposes in the area of nanomedicine.

To put this into perspective, and to pave the way for the prognostication part, it has become increasingly obvious, at least to me, that success with biomaterials-based medical devices is generally achieved when the material is maximally inert, from chemical

and biological perspectives. With so much discussion about 'smart' materials, it is worth considering that the smartest materials are the most inert materials, since they may passively avoid the defenses of the human body. Indeed, the evidence suggests that, through following this maxim, with most types of implantable device, performance is controlled first by the quality of the surgery, second by the characteristics of the patient, and only third by the nature of the biomaterial. As I have argued recently (Williams DF Biocompatibility pathways: Biomaterials-induced sterile inflammation, mechanotransduction and principles of biocompatibility control, ACS Biomaterials Science and Engineering 2017,3(1),2-35), the ability to achieve better performance, especially in newer technologies such as tissue engineering and contrast agents, is dependent on a better understanding of the mechanisms of biocompatibility pathways, and the use of this knowledge to control the pathways and the eventual outcome within the host. It is time for the science of biomaterials to catch up with their contribution to health care.

Biomaterials new frontiers: from synthesis to engineering

Biocues–tethered biomaterials and their future applications

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State-of-the-art of the biomaterial science: basic knowledge and R&D

Implantable materials have made an enormous impact on the treatment of injury and disease of the human body throughout time, particularly after the initiation of aseptic surgical techniques in the late 1800's. Simple materials like glass and clothing materials have functioned surprisingly well to replace a damaged human body part as a non-living prosthetic and have increased the quality of life for many patients. As our understanding of developmental biology, disease, and healthy tissue and organ structure and function has improved, the concept of attempting to regenerate damaged tissues with biomaterials rather than simply replacing them emerged. Biomaterials can impact cell function like an extracellular matrix through similar cell-extracellular matrix mechanisms. Cues for proliferation or differentiation can be provided directly by the biomaterials surface chemistry, 2-D features, topography and pore size. As the material degrades, different signals may be presented to the cells from the degradation products of the biomaterial. Degradation products of biomaterials may provide undesirable cell signals; for example, inflammation due

to particulate debris may lead to a complete loss of the newly regenerated tissue.

Translation into clinics/market: successes and limitations

Translation into the clinics/market has been relatively easy for devices made of biomaterials. Widely used biomaterial devices that positively impact human health include metallic and polymeric hip and knee implants, heart valves, stents and contact lenses. Important quality measures include measurements of physical and chemical structure and biocompatibility testing and degradation. Carefully documented and successfully completed in vitro and in vivo animal safety testing is required at the time of application to gain Food and Drug Administration (FDA) approval to begin a human clinical trial. In the last 20 years biomaterials use has been extended from a relatively inert device to an active delivery vehicle for biomolecules that guide cell behavior. This blending of aspects of pharmaceutics and engineering within a single product has made FDA regulatory approval of biomaterials combination products more complicated. Biomaterials use as scaffolds for cell therapy also have further complicated translation efforts. Standardized testing and characterization methods that can verify the postulated activity of biomaterials in drug delivery and tissue engineering/cell therapy products is being developed through the International Standards Organization (ISO) and the American Society of Testing and Materials International (ASTM). Since the FDA will accept test results obtained using these standards as part of the package submitted to gain FDA approval, standards may help accelerate the FDA approval process for combination products. Experts from academia and industry and medicine are always being sought out to participate in ASTM (www.astm.org) standards writing.

A vision for the future

The biomaterial surface plays a critical role in determining

tissue–biomaterial interactions and this concept has governed the development of many new surface modification techniques that continue to increase efficacy of biomaterials. Surface modification thus remains an important area for research in biomaterials and includes surface modification of diagnostic implants seeking to detect variations in the health status of a person. Biomaterial surfaces that support organ-on-a-chip technology by providing tissue specific cues that mimic extracellular matrix guidance of the development and maintenance of various tissues are also needed. The use of nanomaterials to deliver biomolecules systemically in a targeted fashion based on the presentation of cell specific ligands to cells requiring the therapeutic will be a continued area of growth within the biomaterials industry. Biomimetic design of biomaterial scaffolds with the ability to spatially and temporally control delivery of multiple growth factors is another futuristic product design feature. Tissue regeneration can be optimized by sequential presentation of biological cues to cells, rather than co-delivery, in order to most efficiently guide cells along a differentiation or de-differentiation pathway. Despite extensive research at top hospitals and universities and corporations around the world, there are still many unanswered questions regarding the biological response to biomaterials and the optimal role of biomaterials in tissue regeneration. New discoveries in biological research; such as human embryonic stem cells and CRISPR/Cas9 technology for genome editing, will continue to motivate biomaterials research and new product inventions of the future.

Bioceramics and the worlds of meso, micro and nanoscale

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Background

Nowadays, the prefix bio before the term materials has given rise to the incursion of biology in fields as important as engineering, food and health. Biomaterials are classified within the field of biomedical engineering and combine knowledge from the worlds of science, engineering, biology and medicine. The evolution of medicine has gone from intuition to evidence and is now evolving towards prediction, using computer data in clinical records, which aims to reach a personalized medicine; hence it requires knowledge of mathematics. The evolution of biomaterials in the last 70 years has also been remarkable. The shift from using inert materials to replace living tissue, towards the design of bioactive, biodegradable materials aimed at repairing said tissues, has led to a third generation of biomaterials where the emphasis is in tissue and organ regeneration. This evolution, in a relatively short time lapse, has changed many concepts. The qualitative shift from replace to repair is already surpassed by the idea of regeneration. First generation biomaterials were not specifically designed to interact with the biology world; third generation biomaterials, on the other hand, are designed taking into account their subsequent contact with living tissues and that surface properties of said materials, such as topography, surface charge and all aspects of surface chemistry, play a pivotal role in obtaining a positive outcome when these materials are

implanted among living tissue. This entails a proper functionalization of the free surfaces of these biomaterials, to facilitate cell adhesion, proliferation and differentiation in optimal conditions

Bioceramics

Since the 1950s up to the early 21st century, ceramics have evolved significantly. By mid-20th century, inert ceramics began to be used as replacement of damaged parts of the human skeleton. Only a few ceramics, not specifically designed for biomedical applications –such as alumina and zirconium-, were used. Nowadays, in the 21st century, those bioceramics in clinical use are all specifically designed to repair and regenerate the human skeleton, and several commercial products are in supply for traumatology and maxillofacial surgeons, providing different types of bioceramics. We may consider all these commercially available products as 'traditional' bioceramics, i.e. can be used with all applicable regulations and homologations for this kind of prostheses, fulfilling real and specific needs in the clinical field. Other materials, the so called 'new bioceramics', are instead at the frontier of knowledge; specifically designed for a given function, they will have real applications in the near future and are still a promise.

Evolution in Bioceramics

Third generation bioceramics are used to build scaffolds which support cells performing the regeneration process. Ideally, from the perspective of tissue engineering, said scaffolds should provide mechanical support and biocompatibility, without any induced negative tissue response and with temporary mechanical load bearing capability. In this sense, its degradation rate should be as close as possible to the tissue regeneration rate, interconnected porosity with an optimum pore size distribution, promoting cell and tissue colonization, metabolite transit while offering a high surface area for cell anchoring. There have been great advances in these requirements; four dimensional (4D) printing, for instance, is an emerging technology in tissue and

organ engineering which is based in multi-material reprogramming, capable of changing form, function and/or properties trying to adapt to the environment. In the specific issue of tissue and organ regeneration applications, printing materials must be biocompatible and able to perform 4D dynamic processes in a physiological environment. There is still a long road to go, with great requirements of scientific and technological workloads, but 4D printing can clearly be a powerful tool in the future to carry out biomedical studies of functional synthetic organs and tissues.

The nano- prefix in biomaterials

The emergence of nanoscience and nanotechnology as areas of enormous interest in research is experiencing a dramatic development.
Advances in the preparation of nano-systems with applications in the field of medicine have given rise to new challenges in the design of smart materials capable of responding to new clinical requirements, and various types of ceramic nanoparticles play an important role in this context.
A common concern in medicine is to be able to administer therapeutic agents to the patient through a physiologically more acceptable route. In many cases, the dosages are excessively high, but are prescribed to ensure that the minimum required dose reaches the area where it is needed. But most of the dose administered to the patient, or should we say nearly all of it, acts throughout the whole body, affecting regions where it should not be acting. Therefore, large doses are required in many cases because the drug is released along the way, not specifically, and in areas where it is not necessary. This problem is exacerbated in oncology treatments, where the risk-benefit ratio associated with chemotherapy often makes it difficult to take a wise decision, as a consequence of the cytotoxicity of the drugs to be used. It is generally accepted that the absorption of the drug by the body is favored by its smaller size and by the overlay or packaging material used. A local and smart drug release would be

the answer to these issues. The main advantage of many nano- or microparticles, such as silica mesoporous particles, is their potential multifunctionality. Among the different functions that can be simultaneously achieved we may highlight the following: Load and subsequent release of different drugs, anchoring of biomolecules such as proteins, vectoring agents or nucleic acids to the external surface of the particle and towards therapeutic targets, anchoring of fluorescent molecules or active complexes for magnetic resonance imaging (MRI) in order to perform optical monitoring, inclusion of magnetic nanoparticles, coating with different materials such as certain polymers or metals such as gold.

The Road to the Future

The future development in biomaterials, both in the form of prostheses or replacement parts and as nanoparticles, will require all of these size scales: PICO, NANO, MICRO and MACRO, while molecular and cell biology will provide solutions to clinical problems. Biomaterials porosity should be analyzed at all size scales, in order to understand them and offer new solutions to specific issues. New and future technologies will provide new solutions, and the use of cell-free organs as scaffolds could, with time, be the answer to many problems. The development of biomaterials in 70 years has been astonishing, and it is clear that it will not stop in the near future. Thanks to the advances in molecular and cell biology, these last three decades have been devoted to intensive efforts in regenerative medicine to promote autonomous regeneration of a damaged organ in the body, something already observed in certain species –such as the salamander- but never in humans. Certainly, we are on the right path.

Biocomposites as driving model for future therapy strategy

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Anatomic structures consist of a composite of hard and soft tissues that differ drastically in composition, structure, and properties, and yet integrate and function in synchrony. Because of their ability to mimic the extracellular matrix structure, composite biomaterials have been developed to solve clinical cases in which non-healing conditions prevent tissue repair. Nature-inspired material science can be considered as the last frontier in biomaterials research: indeed, the design of complex structural architectures from sub-micronic to nanometric dimensional scale allows geometrically and topologically mimicking the native state of extracellular matrix and its complex supramolecular assemblies. Composites, Nanofibrous & gel scaffolds could be used to mimic the fibrillar structure of ECM, and provide essential cues for cellular organization, survival and function.

Composite materials with polymeric matrix emerged as strong candidate to substitute metals and ceramics for many applications and lately transferred to the biomedical application. Polymer composites found their applications in load bearing applications (such as hip joint, plates, cages) and as scaffold for tissue engineering and structures for advanced therapy medicine.

Tremendous advances has been made in the composite materials and technologies to design complex structures. Many synthetic and natural polymers, biodegradable and not, have been introduced. Biomaterials, in form of matrix and reinforcement (fibre and particles) were synthesized to control specific material properties (i.e. hydrophilic/hydrophobic domains, mechanical, degradation, etc.) and to modulate the biosignals through chemical and surface modification with biomolecules (i.e. peptides, amino acids, etc.), to mimic the environment of living tissue.

Thus, the biocomposites may be considered at the centre of any successful regenerative medicine strategy and provides many essential features and cues to direct the cells toward a functional outcome.

Modern medicine is based on the implementation of a personalised approach together a less invasive surgery for the restoration of human tissues and organs lost to diseases and trauma, this is forced also by the health care system as the related costs are increasing due to the aging population, for the decrease of birth rate and increase of the life expectancy that is frequently not matched by maintenance of health and quality of life.

More advanced techniques are now available which can clearly produce macromolecular structures of nanometres size with a finely controlled atomic composition and architecture. Polymer chemistry combined with novel processing methodologies such as bioprinting, electrospinning, direct patterning and self-assembly have been used to manufacture nano-composites which can lead to design novel advanced bio-inspired materials able to mimic the different types of extracellular matrices. Nanocomposites are continuously under intense investigation in regenerative medicine to change the physical or chemical properties of biomaterials and guide the activation of specific cellular signalling. This is a unique approach for designing a multi-scale, multi-functional and cell-instructive materials.The design of bio-inspired materials, able to guide therapeutically tissue regeneration and repair remain a challenging goal for the future. Moreover, some phenomena have still to be investigated, the capacity to design and understand the multiscale systems is not sufficient, more effort should be done to analyze the interfaces among the "scale". "Smart sensing" can be a methodology that leverage quantum techniques for use in characterizing subcellular behavior. This includes novel methods in the discovery of ground-breaking basic science that can range investigations at the quantum, atomic and molecular scales within the biological landscape. This should aim to better achieve a clearer understanding of chemical biology and biological physics and subsequently to develop the next generation biocomposites, providing appropriate solutions aid in solving the problems of treating chronic disorders in an aging population by tailoring systems for specific patients and disease states.

References

From bench science to clinics: the tortuous journey of translational research

The biomaterials drift from the clinic (and back to the clinic)

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The field of biomaterials as we know it today started in the clinic. Willem Kolff, M.D., in the late 1930's, using sausage casing, a washing machine and some tin cans, demonstrated that a patient with end stage kidney failure could be revived. John Charnley, M.D., in the late 1940's and early 1950's restored ambulation to patients with failed hips using "modern" materials such as stainless steel and ultrahigh molecular weight polyethylene. Harold Ridley, M.D., also in the late 1940's and early 1950's, addressed cataracts, the most common cause of blindness, with an intraocular lens of poly(methyl methacrylate). About 1950, Arthur B. Voorhees, Jr., M.D., developed the first vascular graft from parachute cloth. Other devices with clinical origin from that time period included the artificial heart, the hydrocephalus shunt, dental endosseous implants and finger joint implants (arthoplasty). All these devices were developed by physicians to meet clinical needs, with the focus on directly impacting patients.

In the 1960s, the words "biomaterial" and "biocompatibility" first appeared in the literature and we saw the launch of a nascent community of scientists and engineers working with physicians on clinical issues. By the 1970s that community spearheaded the formation of the Society For Biomaterials, the European Society for Biomaterials and the The Controlled Release Society. These groups were driven more by scientists and engineers than by physicians (note: clinicians were active in the earliest days of these groups, but leadership soon shifted to engineers and scientists). Basic research on themes relevant to biomaterials was launched in the same time period when these research societies evolved. Subjects such as blood compatibility, protein adsorption, cell interactions, osteogenesis, complement activation, bacterial infection and surface analysis began to dominate our scientific forums.

In parallel with the emphasis shift toward science and engineering occurring in the biomaterials field, the molecular biology revolution happened. Biology transformed from a descriptive science to an intellectual partner with chemistry and physics. The importance of DNA and nucleotides was appreciated. Cytokines and cell surface receptors were discovered. Biology was suddenly mechanistic and amenable to being engineered for specific applications. Biomaterials researchers were quick to embrace these ideas and, to this day, biomaterials meetings are dominated by themes addressing basic science relevant to biomaterials issues. These modern biomaterials research themes, for example, tissue engineering, will lead to stunning advances in the future. But, how far in the future? Given our slow-moving regulatory agencies, challenges in manufacturing and risk aversion in commercialization, these ideas may become important 20 or 30 years in the future.

My opinion is that we need to revive some of the "traditional themes" in biomaterials to make progress in the clinic on a time scale responsive to physician and patient needs. At the University of Washington we have launched a Center for Dialysis Innovation (CDI) to have clinical impact in 5 years in one of the earliest of the biomaterials themes, kidney dialysis.
Why do we need progress in kidney dialysis? Consider this. Kidney hemodialysis originated in Seattle in 1960 where the first successful chronic dialysis took place leading to the world's first dialysis center. Before chronic dialysis people with end-stage renal disease (ESRD) had no options to live beyond about 3 weeks. Chronic dialysis made it possible to sustain the lives of such patients. Now we have some 2,000,000 people worldwide on chronic dialysis. But there are significant concerns. The average lifetime of a patient starting dialysis is 4-5 years due to complications of dialysis. Patients do not feel good while being sustained on dialysis therapy with complications including nausea, itching, fatigue, etc. Dialysis is expensive costing the $100B or more per year worldwide in direct expenses. Finally, due to the expensive and complex nature of dialysis therapy, there are as many as 7.1 million people with ESRD who die each year due to lack of access to this therapy. Little progress has been made in hemodialysis therapy since the 1960's due to an entrenched economic model that does not reward innovation. Many of the complications are associated with "old" biomaterials issues including blood compatibility, biofouling, infection, healing and blood access (thrombosis, blood vessel restenosis).

This opinion paper advocates for an enhanced emphasis on today's patients and for a sharpened focus on clinically-relevant medical devices. We must examine 70 years of biomaterials development and delve into the portfolio of excellent ideas to address immediate clinical issues connected with the human condition and economic stresses on our healthcare systems. The biomaterials of the future must be developed – many of these will trace their roots to tissue engineering and nanotechnology. But, there must also be increased emphasis on what we can do, in the short term, to bring biomaterials research back to the clinic and back to improving the lives of patients.

The biomaterial science: a clinician–scientist's perspective

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From its inception biomaterial science has been interdisciplinary, as the devices designed and manufactured by material scientists and engineers have to be applied to the patient by clinicians. However, the past three-and-a-half decades have witnessed the birth and development of the fields of Tissue Engineering (TE) and Regenerative Medicine (RegMed), which have expanded this interdisciplinarity in a remarkable fashion. How this has evolved within the individual subjects contributing to biomaterials would breach the limits of the present short essay, so that I will confine my remarks to a few selected areas which reflect the perspective of a clincian-scientist, whose research activity has nevertheless been at the basic science end of the spectrum.

In essence, the biomaterial field can be divided into two major areas of scientific endeavour, namely, the materials and the life sciences. The former encompasses all those branches of science necessary to design, develop and produce biomaterials for the clinic, and thus contains numerous disciplines of engineering, but also chemistry and physics. The life sciences are no less multifaceted than the material sciences, and cover a spectrum from numerous basic sciences such as developmental biology, immunology and the various branches of cell and molecular biology via almost all clinical specialities, both conservative and surgical, through to medical ethics. These individual specialities are listed in order to underline the all-embracing nature of modern biomaterial science. Moreover, there are very good

reasons for this rapid and extensive development.

At the risk of making serious omissions, I would mention three elements of the materials sciences which I regard as particularly promising for medical applications.

First, hydrogels will undoubtedly be of immense help in targeted therapy. According to modern concepts and technologies these can be synthesized with responsive, instructive and resorbable characteristics, having the ability to release biologically active molecules under microenvironmental control, for example, released cellular enzymes.

Second, nanotechnology, and in particular, nanoparticles, carry the hope of being able to help diagnose, treat and monitor disease, the „theranostic" concept. Third, rapid prototyping offers the technology to use patient-specific imaging data (e.g. CT, MRT) to build anatomically correct structures for replacement or regeneration which could be used with or without the patient's own (autologous) cells.
In the life sciences the advent and rapid growth of stem cell biology in all its facets have taken regenerative medicine from wishful thinking to reality.

Naturally, there are many regenerative niches in the human body which are still only understood in a very rudimentary way, and include the brain and heart, both organs with a great clinical demand for effective healing. However, progress in live cell imaging has provided a functional tool to investigate niches in the living organism. Models in vitro need to continue their development towards more complex in vivo-like systems and include the exciting field of co-cultures. A further challenge for life scientists is to be found in the need to establish disease models, both in vitro and in vivo. For the former, induced pluripotent stem cells (iPS cells) will undoubtedly be one of the platforms for progress, whilst in the latter successful establishment of disease models in suitable experimental animals will make in vivo experimentation more akin to the real human disease situation.

Currently, most models in vivo still use healthy animals.

Finally, if we are to take biomaterial science into the translational phase we need much more integration of clinicians ab initio into the biomaterial research programmes, as the meaningful pathway begins with the clinician describing what the clinical problem is.

The expertise of the material scientist will then hopefully bring a translatable solution.

Understanding the state of translational research in biomaterials in Europe: A stakeholder perspective

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The research conducted in October 2016-January 2017 illuminates some interesting and challenging issues for translational research in biomaterials.

The outstanding finding is the low involvement of patient groups reported as 2.10% across all the projects reported by stakeholders. The highest involvement being cited in cell based therapies and here the response was only 7.10%. Given that 83% stakeholder respondents indicated that public funding supported their research be that directly (50%) or indirectly through European Research Fellowship Grants (17%), charities (3%) or private / public partnerships (11%) it is a surprisingly low level of engagement with patients and the public who are either the beneficiaries of the proposed research or who are funding the research albeit indirectly, through taxation.

As the questionnaire of the present study was mainly director to team leaders across Europe, the 201 respondents can be considered fairly representative of the biomaterials communities that include an approximate number of 20 major research groups in most countries with the exception of few where the community is relatively small. However, there is sufficient numbers to indicate a trend of low participation by public and patients

when we see they are reporting against 478 projects undertaken across Europe.

This is more surprising when it is clear that it is not only bench scientists who are responding to the survey. This report is about translational work and included projects listed as 'clinical trials' in the following categories: biomaterials for regenerative medicine, tissue engineering, implants, medical devices, drug delivery, cell based therapy, diagnostics and 'other' non-defined projects. All these project categories suggest the 'subject' of the clinical trial would be a patient. The implication is therefore that patient and public involvement in the design, delivery and dissemination of outcomes is missing in 97.9% of the research reported to this survey.

Scientists engaged in applied research have become more familiar with patient and public involvement / engagement (PPI/E) in the design and delivery of research (Dobbs and Whitaker,2016), notably in the UK where the main funder (the National Health Institute for Research, NIHR) has required there to be involvement throughout the research. Indeed, funding is contingent on demonstrating genuine involvement (Involve, 2015). Therefore, a policy push has been effective in driving change in the UK albeit limited to applied scientific research. However, there remains a lack of hard evidence to determine the benefits that patient and public involvement brings to applied research despite drives to capture these data. This is because of variation in the way in which PPI is defined and how the various levels of engagement and involvement are reported (Staniszewska, Adebajo , Barber, Beresford, Brady, Brett, et al. 2011). Fundamental questions remain as to whether PPI can be accurately measured (Staniszewska, Adebajo , Barber, Beresford , Brady , Brett , et al. (2011). So a legitimate challenge is why should scientists be engaged if the PPI/E community and the social scientists who research participation are at odds with one another? Here we nudge at an epistemological and ontological debate with regard 'evidence and legitimacy' that can of itself be circuitous and serve only to furnish the vocabulary of critique

rather than a willingness to engage with the public and patients for whom the biomaterials science is intended.

There are good examples where patients and the public have been involved in priority research setting exercises with the James Lind Alliance, an agency that facilitates points of contact for researchers and PPI representatives, as one example. PPI engagement in priority setting is not without controversy as achieving consensus is complex and challenging especially where the legitimacy of the participants who are representing patient groups and for what purpose can be challenged (Hunter, Kieslich, Littlejohns, Staniszewska, Tumilty, Weale, Williams, 2016). However, there is strong, unrefuted evidence that front end PPI engagement facilitates the accessibility of research materials and helps to shape recruitment strategies (Brett, Staniszewska, Mockford Herron-Marx, Hughes, Tysal, Suleman, 2014 a).

The evidence is weak and largely anecdotal when it comes to bench scientists working with PPI. However, the importance of working with the people for whom the research is intended to drive the bench scientists' enthusiasm and sustain their motivation when the laboratory work is found to be challenging has been highlighted. Patient and public involvement also enables scientists to reflect on their public engagement, find better ways in which to communicate lay accounts of their work and consider the broader moral and ethical issues inherent in their research (Brett, Staniszewska, Mockford, Herron-Marx , Hughes, Tysal, Suleman, 2014 b).

Basic scientists may be more reluctant to engage in these activities because they perceive their work to be too specialist or too complex to be understood by anyone outside their disciplinary community (Dobbs and Warwick, 2016). They might hold that patient and public involvement is not considered relevant to their science, that consultation might introduce confounding variables to their work and risk the introduction of bias that could only serve as a distraction rather than a benefit to their

productivity. Simply, biomaterials scientists might not like what they hear when they consult the public but avoidance is only deferring the inevitable.

Non engagement in the short term can be rationalised as having a lack of money and time to authentically engage in PPI (Brett, Staniszewska, Mockford, Herron-Marx, Hughes, Tysal, Suleman, 2014 b).In the longer term no such reasoning will be considered viable. Projects have to be designed with PPI/E in mind and include robust costings to ensure this can be done effectively throughout the research project. To do this requires a change in attitude and a fresh approach to challenge the status quo. Good science demands good communication and contemporary practice requires dissemination using alternative media beyond the academic journal. Traditional researcher training may not have equipped the scientist with such skills. Socialisation of generations of scientists through technical supervision might have contributed to entrenched positions to avoid patient and public involvement.

In the past, dedication to a research career in biomaterials science to the exclusion of any other 'distraction', including wider researcher development might have served individual scientists and their direct disciplinary community well. Indeed, the Ingenio survey (2016), cites writing scientific articles, preparing research proposals, and laboratory work as the primary job tasks of the respondents. This suggests a knowing of biomaterials solely from the perspective of biomaterial science. Such an approach serves to retain a mystique that maintains the exclusivity of its elite membership, but, is this a viable option in contemporary society? Is this a sustainable position when inter disciplinarity to advance science is promulgated by funders and policy makers (add the industrial partners stuff reference from Monday)?

The results from this survey of 201 European biomaterials scientists implies that time is ripe for change. There will be a requirement to change as more funders require evidence of patient

and public involvement in the design and delivery of research, lay representation of the science and lay accounts of the pathway to impact the research will track. The biomaterials community will have to engage with people outside their direct scientific network as the public demands to know more about the research that is being undertaken to improve their wellbeing and health funded by the public purse. That pressure will intensify as the moral and social issues that surround the potential outcomes of the research become apparent. it is time to awaken to ways in which such political influence can empower the scientists and involve communities in our basic science. This does require a different way of thinking – but who better to help facilitate that than the patients and public for whom the research is both for and about? One model of doing this is presented below.

A new model of patient and public involvement in research known as the beneficiaries model is being developed. This approach places patients, the public alongside clinicians (nurses, allied health professionals and medical staff) and scientists together so they can learn from one another to facilitate involvement in research and public engagement. The novelty is in engaging and involving all three partners from setting research priorities to research design and application (Stewart, 2016). The literature reports PPI occurring as a bipartite relationship between a clinician and PPI or the researcher and PPI (Brett J, Staniszewska S, Mockford et al, 2014b) not with an ambition to engage all three parties from start to finish.

This work has to emerge out of research collaboration with multi-disciplinary colleagues working in the biomaterial research. Such a method should establish a forum that solicits financial, political and human debate about the place of innovative treatments in our society and in turn on the global community. This should include discussion about what is considered morally acceptable, feasible and ethical alongside engaging the patients and their families about the acceptability of the science that is being proposed.

In the past beneficiaries of such an approach were considered to be the persons for whom the treatment was being developed. Here we propose that everyone is a beneficiary. The full extent and range of those benefits is the subject of further research.

This model of PPI has recently been generated through a knowledge exchange conference hosted by the University of Brighton which was attended by key stakeholders including clinicians, bench scientists and the public. The emergent values that were established at the conference are realized and sustained by continuing participation in our bid writing, reviewing, delivery of research, co-production of research and dissemination of research materials and public engagement activities. At each point there is a tripartite meeting of clinicians, researchers and the patient and public. The beneficiaries model further distinguishes itself because we have created different roles within our network of experts (patients, the public, clinicians and researchers) who can be called upon to work with teams of researchers from inception of research proposals to the dissemination of research and all stages in between, but also who actively participate in our wider public engagement activities. Interdisciplinary teams are established that cross social science, the arts and humanities as well as life health and physical sciences and incorporate a network of the public and patients who can participate in our diverse range of activities according to their area of interest. Their legitimacy determined by their commitment to participate, not solely because of a vested interest. An ever widening panel of interested parties ensure that we can reduce the burden that might otherwise fall to a few individuals.

This is not easy. Nurturing the enthusiasm beyond initial interest and seeing this through to completion of a project does require attention. Here it is recommended that this work package be facilitated by a named person, be that a colleague outside the biomedical science community or a scientist who is keen to foster this work. However, one important but unreported

resistance might be the personality of the scientist and how they were drawn to bench science in the first instance: a talent for maths, chemistry and or physics rather than social science, the arts or humanities. The language of science potentially limits discussion and the forging of professional relationships with a wider non-academic / outside specialism scientific community unless purposively facilitated. So having an 'outsider' to take the lead on PPI/E in the first instance and to build up the scientists repertoire of skills of effective involvement and engagement is not without challenge. Further, we describe 'working with' not 'devolving to' colleagues if the approach to PPI is to be long term and sustainable.

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Gazing new horizons

The role of ICT in biomaterial research and development

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The history of Biomaterials shows that different civilizations have implanted materials in the human body. The advances in Medicine and Surgery allowed different countries with different political systems to build up their own healthcare systems, public, private or mixed, after the Second World War. Biomaterials became Science and Technology because the need to treat large numbers of patients in these welfare societies produced a large industrial demand of implants. The evolution from substitutive implants, for which the main requirement was their inertness and tolerance in the biological environment, to instructive biomaterials, able to play a key role in regenerative therapies, has taken place in the last thirty years. With the advent of what is called the 4th industrial revolution, the evolution of the incremental knowledge generated in Biomaterials Science and Technology seems assured. This does not necessarily mean that the industrial/clinical successes will increase. The low rate of industrial achievements coming from the European Commission funding in Biomaterials research projects is a good example. Probably, new views could come to favour new approaches.

The idea that Information will take humanity towards an Informational Society, as Industry took it to the Industrial Society, was published by Manuel Castells (1996). Industry changed totally society in terms of economy, work, social relations, family, etc. Castells' thesis is that something similar is going to happen with Information. In terms of higher education and research, Industry transformed universities. Previously non-existing high level professional degrees became strongly necessary and demanded: engineering, economics, psychology, etc. The need to generate not only knowledge but also diverse know-how changed the focus on education, and boosted as well the need for research to be transferred to industry and to the economic and social world.

Information and ICTs have started to transform our way of living and our society. The changes in the photography and music industries are now fully recognizable and there are clear signs that the automobile industry will come next. Big Data and more specifically the application of the theory of complexity may change our way to address scientific problems. The concept of Emergence in complexity means that the whole is more than the sum of the parts and this is what happens in biology and life. The reductionist approach applied in molecular biology research has greatly benefited the spectacular evolution of Biology. The theory of complexity brings holistic views that are substantiated in what is called systems biology. At present, Machine Learning or Artificial Intelligence is being applied with success in regenerative medicine research, such as obtaining a regeneration model for planarian, creating tadpoles with pigmentation non-existing in nature, analysing patterned differentiation of mesenchymal stem cells, or predicting stem cells knee arthritis outcomes. Artificial intelligence and machine learning are becoming an integrated part of life science research. There is increasing evidence that we are moving towards an algorithmic theory of biology.

The important issue is then to understand how such holistic approaches are going to change our scientific way of thinking. If scientific methodology does not need to be only reductionist, then regenerative medicine and more specifically, biomaterials for regenerative therapies could be designed according to the complexity existing in biological systems. Biomaterials researchers will be able to develop their work faster and in a more informed and accurate manner.

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