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The Winner Takes It All: Stance and Engagement Markers in ERC Funded Projects' Summaries

Thesis submitted in partial fulfilment of requirements for the degree of BA in English Philology

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Table of Contents

Abstract

This paper aims to investigate differences in the use of stance and engagement markers between different science fields in research proposal summaries. For this comparative, corpus-based, quantitative and qualitative study, Hyland's (2005b) framework of stance and engagement was chosen to analyse and compare different science fields in European Research Council funded project's summaries. Three science fields analysed in this paper were social sciences & humanities, life sciences and physical sciences & engineering. A corpus consisting 90 project proposal summaries was compiled and each text was manually examined for stance and engagement markers. The results show that, overall, stance markers were used much more frequently than engagement markers in all science fields analysed. However, compared to writers of social sciences & humanities, it was found that writers of life sciences and physical sciences & engineering tend to use more stance markers which implies that they find it more important to stand out as researchers in the text, focussing more on creating a stronger authorial persona. For social sciences & humanities, on the other hand, it was noticed that the writers used more engagement markers than the writers of the other two science fields, which implies that their texts are slightly more reader focused, drawing the readers more closely into the discourse in order to guide them through the presentation of the project.

1. Introduction

Academic discourse has received a considerable amount of attention in the last three decades (Pho 2013). Written academic discourse, in particular, has been analysed from a large number of perspectives (Yang 2014). As an integral part of university education and scientific research in general, academic texts have been studied in order to educate university students and academics in academic writing (Hyland 2004; 2009). In addition, authors also study academic texts not only to teach academic writing but also to describe different genres of it (Swales 2004; Swales and Feak 2009). A genre of academic text that readers of research articles most often notice first is the abstract. Bondi and Lores Sanz consider abstract a key element of a research paper because it is not simply a part of the text but a representation of the whole paper (2014). Thus, an abstract informs the reader about what to expect in the paper. Furthermore, Ngai and Singh see the purpose of abstracts as to "convince readers that the article is worth reading" (2020:1). Therefore, the abstract stands on its own and is a key element of an article.

Same as other genres of academic texts, abstracts have been studied from a number of perspectives. Among them, functional structure of abstracts (Pho 2013; Zibalas and Šinkūnienė 2019), instructions on how to write abstracts (Swales & Feak 2009) and metadiscoursal elements in abstracts (Diani 2014; Ngai and Singh 2020; Rashidi and Alihosseini 2012). Metadiscourse and metadiscoursal elements in academic writing, as an area of discourse studies, focuses on the relationships between the writer, the text and the reader (Hyland 2005a). From a metadiscoursal perspective, Hyland argues that what writers of academic texts do is "engage in a web of professional and social associations" (2000:1). That means that the goal of an academic text is not only to present a study but also to interact with members of academia that read it. As the medium in case of academic writing is written text, a writer can achieve their communicational goal through making more careful lexical choices, quoting or paraphrasing other authors as well as making other moves.

A framework for studying writer to reader interaction, which has been applied in a large number of linguistic analyses for the past two decades, was proposed by Hyland (2005b). It considers texts lexically by examining two aspects that the author finds tangible as well as highly meaningful (Hyland 2005b). The two aspects are stance, which "can be seen as an attitudinal dimension", and engagement, through which writers "acknowledge and connect" to their readers (Hyland 2005b:176). In other words, stance is embodied in writer's lexical choices that help build their authorial persona by conveying their "judgements, opinions, and commitments" (Hyland 2008:5). Engagement, on the other hand, focusses on the reader, acknowledges their presence and includes them in the discourse. Stance and engagement framework offers a

comprehensive way of studying texts because it analyses specific lexical units that could potentially be identified as either stance or engagement markers (McGrath and Kuteeva 2011). Thus, the aforementioned framework has been chosen for this paper.

Existing studies of stance and engagement have often studied academic texts by comparing science fields, notably, hard and soft sciences (Hyland 2005b; McGrath and Kuteeva 2011) or analysing different genres of academic texts (Hyland 2000; 2005b). The latter, despite being rather thoroughly studied already, has not yet analysed all the different genres, which could potentially offer interesting insight into contemporary academic texts. One such genre is the genre of research summaries, closely related to research abstracts.

Katkuvienė and Šeškauskienė define the difference as the summary potentially being longer, and including background information (2006). Summaries have been studied for the last few decades (Bondi and Lores Sanz 2014; Swales and Feak 2009; Swales 2004). The interest of summary genre may lie in the fact that they are rather unique, as they are more standardized than other genres and more detached from the text that they belong to (Bondi and Lores Sanz 2014). Swales and Feak point out that genre restrictions, most notably word limits, have a very strong effect and result in an increased difficulty of writing (2009). This also means that writers have to be more attentive when it comes to the words they choose. Hence, because summaries have to be written more carefully, they are potentially interesting candidates for lexical analyses.

A type of summaries chosen for this study is research proposal summaries. Research proposals are written in order to receive grants and to be able to carry out research. As an academic genre, research proposals have not yet received considerable attention. Tran and Chau, for example, studied metadiscourse markers in postgraduate students' research proposals and outlined the importance of teaching university students to write them (2021). The research proposals analysed in the study carried out by Tran and Chau (2021) were written by postgraduate students. It would also be interesting to study research proposals written by experienced researchers as there are very few such studies. An example of an organisation which offers research grants to experienced researchers is European Research Council, or ERC. It is one of the institutions that offer such grants for researchers with promising careers or histories of valuable research. Projects from all over Europe and from many different disciplines receive grants from ERC as well as substantial financial support in order to carry out scientific studies that might help shape the future of science. Thus, projects that receive grants from ERC might be among some of the best research projects carried out in Europe. For that reason, summaries written for ERC funded projects have been chosen to be analysed for this paper.

In order to study how ERC funded project's summaries, as a genre, use stance and engagement markers, research questions proposed for this study are: Do European Research Council funded projects' summaries use more stance or engagement markers? How are different stance and engagement markers used in summaries of ERC funded projects written for different fields of science? What sub-types of stance and engagement markers are used in summaries of ERC funded projects and how do they describe the different science fields?

2. Data and Methods

For this comparative, corpus-based, quantitative and qualitative study, a corpus was compiled using project summaries from European Research Council's (ERC) database of funded projects[1](2022). The database consists of entries of all projects that have been funded by ERC. All entries in the database include only basic information about each project: their acronym, title, details such as grant type, researcher's name, researcher's host institution and country, and, lastly, summary. Full project proposals are not provided but visitors of the database can read the summary of the project, which includes information, such as the main research problem and aim, prior research done and what the researcher expects to achieve. In addition, all projects are grouped into different categories. The first category is the type of grant received. It includes starting grant, which requires applicants to have 2-7 years of research experience since the completion of their PhD, consolidator grant, which requires applicants to have 7-12 years of research experience since the completion of their PhD, and advanced grant, which requires the applicants to be active researchers with significant research achievements in the last 10 years. The second category is call year, which groups the projects by the year they were proposed. The third category is research domain, or as it will be referred to in this paper, science field. It includes three science fields: social sciences & humanities; life sciences; physical sciences & engineering. The last category is host country and refers to the country where the institution that the researcher is associated to resides.

To compile the corpus for this paper, only a certain type of project summaries were chosen. Firstly, the type of grant received was chosen to be advanced grant as the researchers writing the summaries had to be accomplished scholars, which in turn indicates extensive experience not only in research but most probably in creating academic texts such as summaries. Secondly, the year the projects were proposed was chosen to be the most recent, which at the time of compiling the corpus was 2018 and 2019. Thirdly, the category of host country was chosen to be disregarded because choosing only a certain country might have resulted in a limited number of institutions that dominate certain fields. Lastly, all three science fields were chosen to be analysed. However, an additional problem arose in making sure that the data is fully comparable. Scientific fields, in ERC database, are further divided into unequal number of sub-groups called panels (e.g. *The Study of the Human Past*; *Physiology, Pathophysiology & Endocrinology*; *Fundamental Constituents of Matter*). As the scientific fields contained from 6 to 10 panels, a way to objectively choose projects was devised. From every scientific field, 3

[1] Link to the website of the database - https://erc.europa.eu/projects-figures/erc-funded-projects/results?f%5B0%5D=funding_scheme%3AAdvanced%20Grant%20%28AdG%29

panels with the most projects overall were chosen. From each panel, 10 most recent projects' summaries were taken. Thus, a corpus was compiled containing 90 project summaries from three different science fields, written by accomplished scholars in 2018-2019. The composition of the corpus is shown in table 1. The corpus analysed is provided at the end of this paper as appendix 5. Texts of the three sub-corpora are coded according to scientific field and are assigned a number. Every summary is coded SH for social sciences & humanities, LS for life sciences and PE for physical sciences & engineering. Every example provided in this paper is marked SH, LS or PE plus a number (e.g. SH-11), representing the science field and the number of the summary for easier navigation.

Table 1. Composition of corpus of ERC funded projects' summaries

Sub-corpus	Number of words	Number of summaries
Social sciences & humanities	8,536	30
Life sciences	8,535	30
Physical sciences & engineering	8,710	30
Total	25,781	90

For the analysis of this paper, Hyland's (2005a) framework of stance and engagement was chosen. This framework helps study interaction in academic discourse by investigating specific lexical choices that writers make. As a way of interacting with the reader, stance communicates the writer's attitudes "which refer to the ways writers present themselves and convey their judgements, opinions, and commitments" (Hyland 2005b:176). Engagement, on the other hand, helps the writer "rhetorically recognize the presence of their readers to actively pull them along with the argument, include them as discourse participants, and guide them to interpretations" (Hyland 2008:5). The two ways of interaction are manifested by more specific lexical evidence. The kinds of stance and engagement markers are illustrated in figure 1.

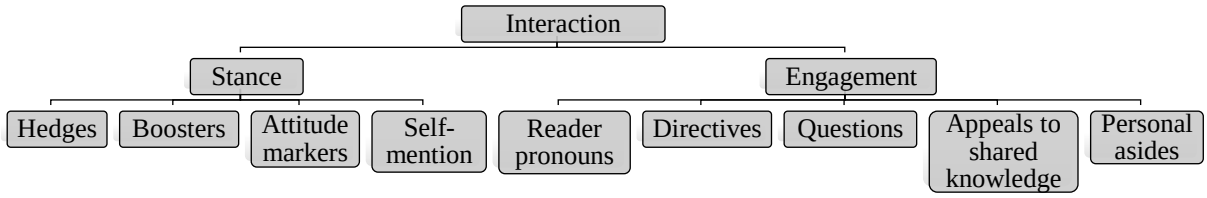

Figure 1. Stance and engagement markers (Hyland 2005b:177)

Each stance and engagement marker shown in figure 1 has a different effect and appears in different form, such as sentence adverbials, modal verbs, adjectives, etc. Below, all stance markers' functions are described and examples for markers that occurred are given from the corpus of ERC funded projects' summaries.

- **Hedges** can make the proposition seem less definite and/or show that the writer is not fully certain or committed to it.

(1) ***Arguably**, the most important function of color is the processing of information about objects in scenes. (SH-2)*

- **Boosters** act oppositely than hedges, making the proposition more definite and/or showing that the writer is certain or committed to it.

(2) *We here propose three **completely** new and high-risk strategies to prevent CMD in large subsets of the population, who have elevated risk due to measurable endocrine abnormalities. (LS-6)*

- **Attitude markers** help the writer express affective attitudes, such as importance, clarity, frustration and other.

(3) *These **groundbreaking** studies should illuminate how conserved signaling pathways work through the nucleolus to regulate health and life span. (LS-30)*

- **Self-mention** explicitly creates the presence of an author in the text.

(4) ***We** propose to design and build switchable synthetic molecules that are capable of communicating and processing information. (PE-13)*

- **Reader pronouns** create the reader's presence in the text, including them into the discourse.

(5) *Human thoughts have no mass and remain definitely hidden from others' view. Still, **we** are remarkable at predicting others' mental states from observable phenomena. (SH-7)*

- **Directives** instruct the reader to perform a certain textual, physical or mental act.

- **Questions** create a dialogue between the writer and the reader, presenting, for example, problems or aims.

(6) ***But what of the fundamental, functional cellular building block of this architecture – the single neuron and its dendritic tree?*** *(LS-18)*

- **Appeals to shared knowledge** signal that a piece of information is likely to be familiar or even agreed upon.

(7) *History has* ***traditionally*** *prioritised literary texts, creating a Helleno- and Romanocentric narrative, which often relegates the island to a footnote. (SH-14)*

- **Personal asides** allow readers to interrupt the text and to offer a personal comment in the shape of an imitated dialogue.

Moving on to the analysis, stance and engagement markers were identified manually as each summary from the corpus was closely read. Later, for the identification of more specific sub-types of stance and engagement markers, all the texts were read once again manually and different stance and engagement markers were grouped into tables which can be seen in appendices 1-4. For quantitative analysis of the data, all occurrence frequency numbers were normalized into occurrences per 1000 words. For accurate comparison of frequencies, log-likelihood test was used. The test determined if a difference between two frequencies was statistically significant. According to McEnery and Hardie, in order for the frequencies of occurrence to be significant, a log-likelihood score at $p < 0.05$ level has to be higher than 3.8 (2012). Thus, all occurrence differences that are indicated to be statistically significant, are tested according to log-likelihood test. For that, a publicly-available log-likelihood counter was used from Lancaster University's website[2]. Then, the data was qualitatively analysed according to stance and engagement framework (Hyland 2005b) and by comparing to other studies mentioned in the next section of this paper.

[2] Link to the website of the calculator - http://corpora.lancs.ac.uk/clmtp/2-stat.php

3. Results and Discussion

3.1. Overall distribution of stance and engagement markers

Firstly, the numbers of stance and engagement markers in all three sub-corpora will be discussed in order to see whether stance or engagement was a more prevailing aspect of the texts analysed. Then, difference of use of the markers across the three sub-corpora will be examined to find differences between the three scientific fields: social sciences and humanities; life sciences; physical sciences and engineering.

Table 2 below shows that in the whole corpus, there were around ten times more stance than engagement markers.

Table 2. Overall distribution of stance and engagement markers (per 1000 words)

Type of marker	Social sciences & humanities sub-corpus	Life sciences sub-corpus	Physical sciences & engineering sub-corpus	Total
Stance	23.2	47.6	38.3	36.4
Engagement	6.3	2.6	2.0	3.6

Similar results were also found in most other studies that compared frequencies of stance and engagement markers in academic texts. Hyland (2005b), for example, found stance markers to be five times more common than engagement markers in full research articles. Alghazo et al. (2021) studied research paper abstracts, a genre similar to summaries, and found that all types of engagement markers made up only 3% of all stance and engagement markers. Both the results of this paper's analysis and the results of Alghazo et al. (2021) show that academic summaries and abstracts might show an even greater difference between the use of stance and engagement markers than research articles.

However, another study that analysed stance and engagement markers in pure mathematics research articles found that engagement markers were around three times more common than stance markers (McGraft and Kuteeva 2011). This discrepancy might signal a difference between science fields as McGrath and Kuteeva (2011) studied hard sciences' texts. However, as can be seen in table 2, physical sciences & engineering sub-corpus, the closest representative of hard science, had even more stance markers compared to engagement markers than corpus average. Thus, the contrasting results found by McGrath and Kuteeva (2011) do not correspond to the results of this study but signal that there might be differences in the use of stance and engagement markers between different science fields.

Shifting the focus towards the differences of science fields, the differences of use of stance and engagement markers was lowest in social sciences & humanities, where there were almost four times more stance markers than engagement markers. This difference, even though the lowest among the three science fields, was already significant according to log-likelihood test. In the other two science fields, physical sciences & engineering and life sciences, the difference was even greater, showing that these writers used more stance markers as well as fewer engagement markers than social sciences & humanities. Generally, the differences illustrated in table 2 might suggest that the writers of all of the science fields analysed used significantly more stance markers than engagement markers but that difference was smaller in social sciences & humanities. The larger share of stance markers may suggest that for writers of ERC funded summaries it is important to build their authorial persona. The texts are relatively short and it is imperative that the author stands out among the other candidates to receive ERC grants. The lower number of engagement markers seems to suggest that leading the reader through the interpretations is less important. That does not seem unexpected because of the short length of summaries. Unlike with a full scientific article, a reader can read a summary quickly, and help in reading through different interpretations is not necessary because a summary is not only a short genre but also a very direct one. It presents only the most essential information. Yet, as the same results were found by most but not all studies discussed, it is important to further analyse the differences between science fields by focussing on the use of different stance and engagement markers and their use among different science fields.

3.2. Distribution of stance markers between science fields

For further analysis, this section will discuss with how stance markers occurred in different science fields. In addition to that, different sub-types of stance markers found in the corpus will be identified and discussed. As can be seen in table 3 below, attitude markers were the most frequently occurring stance markers. Thus, I will begin by discussing them and later move on to the less frequently occurred markers.

Table 3. Stance markers by science field (occurrences per 1000 words)

Stance marker	Social sciences & humanities	Life sciences	Physical sciences & engineering	Total
Attitude markers	13.4	23.1	24.8	20.4
Self-mention	3.2	15.9	5.9	8.3
Boosters	3.3	4.3	4.8	4.2
Hedges	3.4	4.3	2.9	3.5

3.2.1. Attitude markers

Attitude markers were used significantly differently across the three science fields. Table 3 shows that the greatest differences between the use of attitude markers were between the social sciences & humanities and physical sciences & engineering sub-corpora. As demonstrated in table 4 below, the difference between the two sub-corpora was found to be significant, with the log-likelihood score of 30.0. The same can be said about the difference between sub-corpora of Social sciences & humanities and Life sciences. The difference was not significant between Life sciences and Physical sciences & engineering sub-corpora.

Table 4. Log-likelihood scores for differences between the uses of sub-types of attitude markers

Sub-corpora compared		Log-likelihood score
Social sciences & humanities	Physical sciences & engineering	30.0
Social sciences & humanities	Life sciences	22.4
Life sciences	Physical sciences & engineering	0.5

Attitude markers convey the writer's affective attitude towards prepositions and indicate, for example, that the writer finds something important or surprising. The results in table 4 indicate is that both in physical sciences & engineering and life sciences it was far more important for the authors to convey their affective attitude. Once again, rather different results were found by McGrath and Kuteeva (2011) as they found attitude markers to occur significantly less frequently in their study of pure mathematics research articles. Yet, the authors still admit that attitude markers "play an important part in the creation of a credible authorial persona" (2011:167) and thus it can be said that they play an even more important role in ERC funded projects' summaries, most notably in life sciences and physical sciences & engineering fields.

3.2.2. Main sub-types of attitude markers

Attitude markers signal the writer's affective stance on the prepositions. Scholars identify rather different sets of affective meanings that attitude markers convey in their corpora. Most, if not all, sets include the sub-type of 'other' that includes more specific meanings that are not as easily analysed and grouped (Hyland 2005b; Sayah and Hashemi 2014). The sets of meanings of attitude markers thus largely depend on the corpus of the study. The corpus of ERC funded projects' summaries is no different in this respect. Although not completely fixed, the types of meaning conveyed by the attitude markers found in this study can be seen in figure 2. In addition, a full list of all attitude markers identified by sub-type can be found in appendix 1.

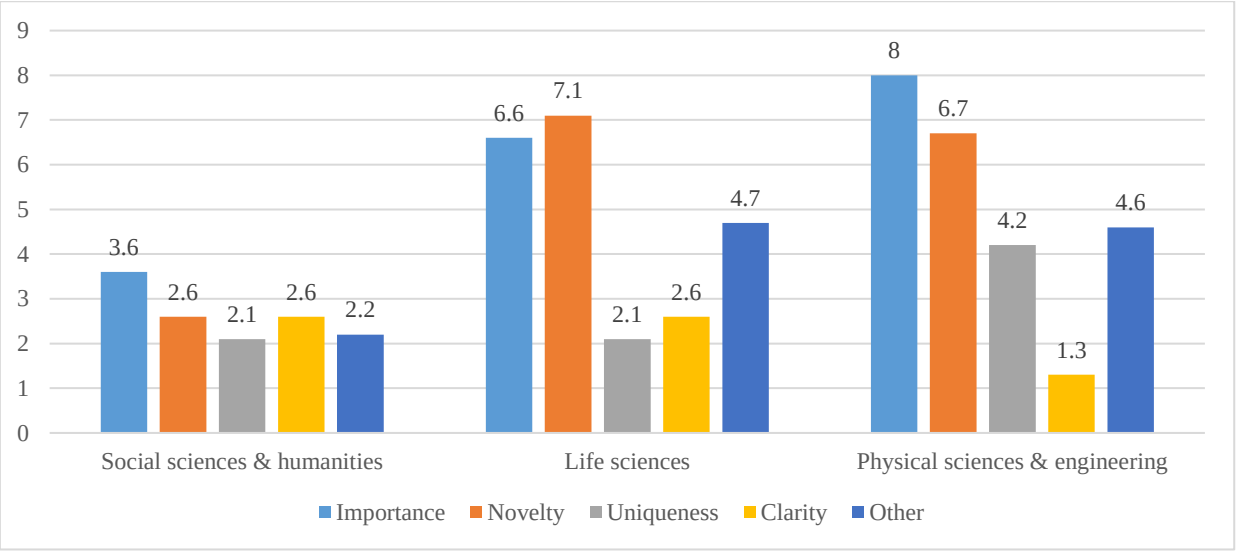

Figure 2. Sub-types of attitude markers by science field (occurrences per 1000 words)

The main types of meanings conveyed by attitude markers, as shown in figure 2, are importance and novelty. Importance and novelty were among two most used meanings in every scientific field. However, in social sciences & humanities importance and novelty were not significantly more frequent. The log-likelihood score between importance, the most frequently used meaning, and uniqueness, the least frequent meaning, was 3.5 and did not qualify as significant. In fact, the frequencies of all meanings conveyed by attitude markers in social sciences & humanities sub-corpus were similar as a significant difference according to log-likelihood was not found between any of them. In life sciences and physical sciences & engineering, on the other hand, importance and novelty were significantly more frequent than the other meanings. It indicates that it was highly important for the writers to describe the methods used and the problems faced by their projects as innovative and essential for their fields of research. As the use of attitude markers signals, it is most important for the fields of life sciences and physical sciences & engineering to stand out among other researchers and researcher teams. Thus, using attitude markers pointing to novelty and importance of their research, the writers try to set themselves apart from the competition. Examples (8) and (9) illustrate these effects.

(8) *Obtaining reliable cross sections for neutron-induced reactions on unstable nuclei is a highly* ***important*** *task and a major challenge. (PE-7)*

(9) *We provide completely* ***novel****, mechanism-orientated and near-future applicable strategies for primary prevention of CMD. (LS-6)*

Example (8) implies that the *task* described is *highly important*. As it is the main aim of that project, the writer calls it *important* in order to make the project seem necessary. In example

(9), the writer claims to *provide strategies* that are completely *novel* and therefore possibly able to provide a solution to a yet unsolved problem.

Moving on to uniqueness and clarity, the other two meanings that attitude markers conveyed in the corpus. It is clear from figure 2 that they occurred less frequently than the other two meanings. Writers referred to uniqueness and clarity as frequently in social sciences & humanities as they did in life sciences. In physical sciences & engineering, on the other hand, it was significantly more frequently referred to uniqueness than clarity. Uniqueness, in the corpus of this study, pointed to the fact that a problem, method or finding is not only new, but also one-of-a-kind. This is illustrated by example (10), where the writer promises *unprecedented opportunities to the scientific community*.

*(10) e-DOTS will thus offer **unprecedented** opportunities to the scientific community, since the specific molecular properties of the reactants can be transferred, combined and enhanced up to the nanoscale, yielding carbon nanodots tailored to function. (PE-21)*

The meaning of clarity was a little more complex as it referred to something not only as clear but as unclear as well. It allowed the writers mostly to comment on the complexity of certain problems faced by the project or solutions that either already exist or are yet to be found. Example (11) shows how a writer uses the word *enigmatic* to describe the object of their study as difficult to understand. This communicates to the reader that the object of study has not yet been researched enough and therefore is a suitable candidate for future research. The writer in example (11) plays with academic tradition of seeking yet unfound knowledge, making their project seem necessary.

*(11) The proposed project will focus on precisely that question, in an attempt to unravel what is perhaps the most **enigmatic** episode of 'Great Wall' construction. (SH-19)*

As for the other meanings conveyed by attitude markers in the corpus of ERC funded projects' summaries, there was a high number of unique meanings or meanings that could not have been categorised systematically. As it is not a homogenous and systematic sub-type, no results could be drawn from it.

3.2.3. Self-mention

Self-mention markers were the second most frequently occurring stance marker in the corpus of ERC funded projects' summaries. In this case, the differences of use of self-mention markers between every scientific field were all found to be significant according to log-likelihood test. Ma (2021), after analysing stance and engagement markers in research articles across sixteen different disciplines, found self-mention markers to be one of the main ways of emphasizing

authorial presence. Self-mention markers help accredit the propositions put forward in the text to the author, strengthening their authority. It is clear that in summaries of ERC funded Life sciences projects, authors find it highly important to make themselves stand out as researchers. However, as can be seen in table 3, self-mention markers occurred in rather different frequencies in the three sub-corpora. In life sciences, self-mention occurred 15.9 times per 1000 words but in physical sciences & engineering and social sciences & humanities it occurred only 5.9 and 3.2 times per 1000 words, respectively. What the rather large gap between life sciences sub-corpus and the other sub-corpora could indicate is that the writers working within the field of life sciences find stressing their presence as researchers in the text highly important. The fact that researchers used a high number of self-mention markers might signal that life sciences as a science field is more competitive and relies on individual researchers or teams of researchers instead of the field's gradual development driven by the scientific community. For social sciences & humanities and physical sciences & engineering, on the other hand, standing out seems less important than for life sciences. However, Tran and Chau (2021) found that self-mention markers were the most frequent stance marker used in writing linguistics related research proposals. Tran and Chau (2021) analysed research proposals written by post-graduate students and the summaries in the corpus of this study were written by researchers with extensive experience in their fields. What the opposition might show is that experienced writers carrying out research in the fields of social sciences & humanities and physical sciences & engineering used self-mention markers to a lesser extent because they might not have felt the necessity to do so. That, in turn, might indicate that in the fields of social sciences & humanities and physical sciences & engineering the role of an individual researcher or a team of researchers in not as important as it is in life sciences.

3.2.4. Main sub-types of self-mention

Self-mention markers are a rather specific kind or marker as they are used only to simply create the presence of the author. In the corpus or ERC funded projects' summaries, they occurred in two different types, referring to a single person (I, my) and referring to multiple people (we, us, our). Their distribution can be seen in figure 3. A full list of self-mention markers identified by sub-type can be found in appendix 2.

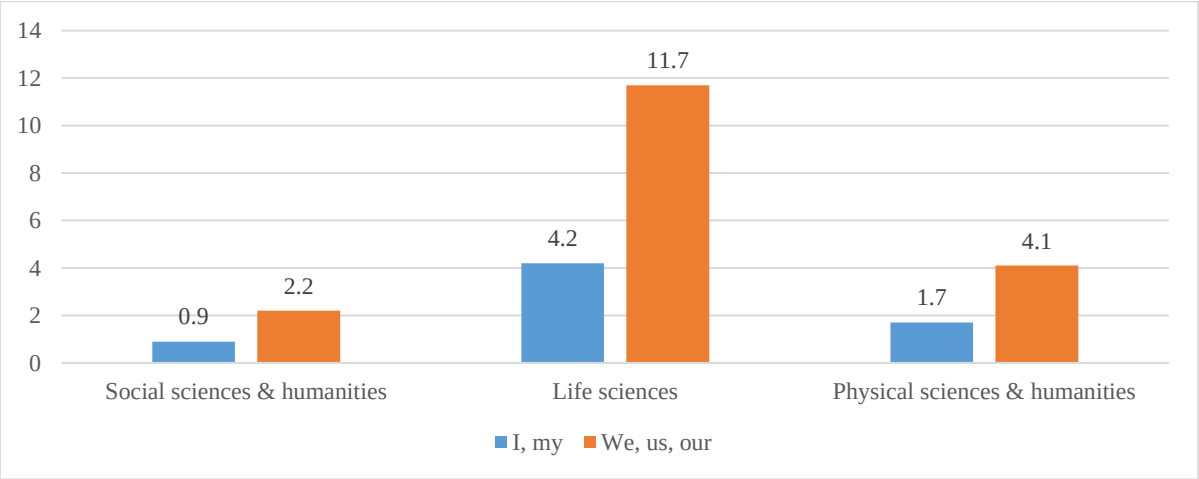

Figure 3. Sub-types of self-mention by science field (occurrences per 1000 words)

Figure 3, shows how the two different sub-types of self-mention markers occurred across the three sub-corpora. Differences between the use of these markers to refer to a single person and to several people, according to log-likelihood test, are statistically significant. It was pointed out earlier that in every scientific field the number of self-mention markers was different. Figure 3 shows that the sub-types of self-mention markers used in different fields occurred similarly in all fields. Writers referred to themselves using 'I' or 'my' significantly less frequently than referring to themselves and their team using 'we', 'us' and 'our'. ERC grants their funds to individual researchers who are responsible for the project but can also employ other researchers. In addition, the researchers who wish to be funded have to be associated to an institution who hosts them. This means that the projects, which are presented in the summaries analysed in this paper, are not expected to be carried out by a single person. Therefore, a significantly larger portion of self-mention markers found, refer to the team of researchers and not an individual author.

3.2.5. Boosters

Hyland describes boosters' role in the text as a way for writers "to express their certainty in what they say and to mark involvement with the topic" (2005b:179). As boosters were among the least frequently occurring stance markers in the corpus of ERC funded projects' summaries, communicating certainty and showing a high level of involvement in the field seems to be a less important effect compared to expressing affective attitude with attitude markers or creating a presence of an author with self-mention markers.

According to log-likelihood test, social sciences & humanities used boosters significantly less frequently than the other two science fields. This could signal that life sciences and physical sciences & engineering find expressing certainty and involvement in the researched field more

important. In turn, this might show that the researcher's knowledge of more precise facts and methods is seen as an advantage in the fields of life sciences and physical sciences & engineering. In addition, precision does not seem as important in social sciences & humanities, perhaps because as a soft field it deals with methods that do not change as rapidly and facts that are not as definite as in the other fields.

3.2.6. Main sub-types of boosters

Boosters, as metadiscoursal markers, appear to have a narrower span of functions than other stance markers in the corpus of ERC funded projects' summaries. There does not seem to be many significant sub-types of boosters that can be categorised apart from a more straightforward division into parts of speech. In the corpus of ERC funded projects' summaries, boosters occurred as either adjectives or adverbs. Figure 4 illustrates the differences of use of adverbs and adjectives as boosters in the corpus. The list of boosters identified by sub-type can be found in appendix 3.

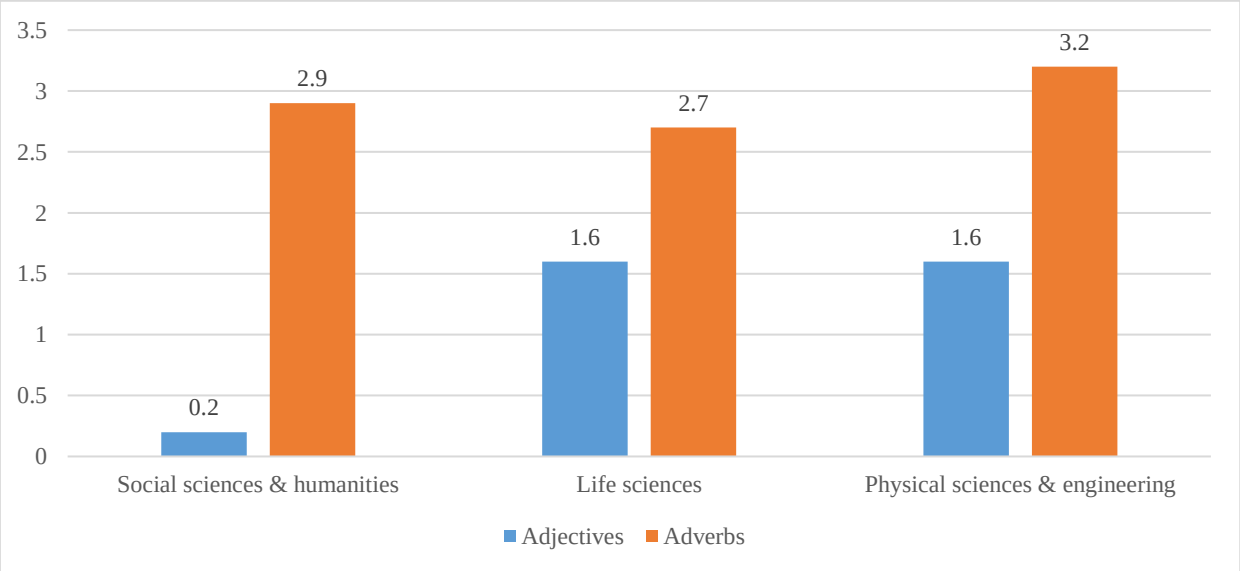

Figure 4. Sub-types of boosters by science field (occurrences per 1000 words)

Boosters appeared as adverbs a similar number of times in all three fields and a statistically significant difference between them was not found. For adjectives, on the other hand, a statistically significant difference was found as they occurred significantly less in social sciences & humanities compared to life sciences and physical sciences & engineering. As this is a purely statistical observation, no obvious conclusions present themselves yet. Another observation, that could be made by looking at the occurrence of boosters as adjectives and adverbs, is that in all three sub-corpora boosters occurred as adjectives only 1.2 times per 1000 words, while occurring as adverbs 2.9 times per 1000 words. Log-likelihood test shows that there is a significant difference between the two frequencies. Biber et al. notes that one of the

difference of adjectives and adverbs is that adjectives occur more frequently in written registers and adverbs occur more frequently in conversation and fiction (1999). This seems peculiar, as it was found that boosters as adverbs, not adjectives, occurred more frequently in the corpus of ERC funded projects' summaries. However, there are no significant clues leading to a more comprehensive comparison between different types of boosters.

3.2.7. Hedges

The effect that hedges have on propositions is described by Hyland as to "withhold complete commitment to a proposition, implying that a claim is based on the writer's plausible reasoning rather than certain knowledge" (2008:7). This effect, however, seems to be rather unimportant as hedges were the least frequently occurring stance marker in the corpus of ERC funded project's summaries. Both in research articles across different science fields analysed by Hyland (2005b) and in social sciences' research article abstracts analysed by Alghazo (2021) hedges were found to be the most frequently occurring stance marker. The dissimilarity between the use of hedges in the summaries analysed in this paper and the other studies mentioned might be one of the distinct features of ERC funded projects' summaries. Academic texts in general, might seem to traditionally exhibit modesty while making claims. Hedges are used, for example, to protect the writer from making sweeping generalisations. In ERC funded projects' summaries, on the other hand, hedges are not used as frequently, especially compared to other stance markers. This could show that the writers of the summaries analysed constructed their texts to show a higher level of certainty in the propositions provided as well as making the propositions seem less of a result of the writer's reasoning and more as a definite fact. Perhaps the specific genre of an ERC funded project's summary requires the researchers to exhibit a high level of certainty in the success of their project in order to receive a research grant.

Difference between the use of hedges between the three science fields analysed in this study was not found to be statistically significant. The difference between life sciences sub-corpus and physical sciences & engineering sub-corpus was chosen to be tested because, as table 3 shows, the difference between occurrence of hedges was greatest between them. The log-likelihood score was found to be 2.2 and therefore showing a statistically insignificant difference.

3.2.8. Main sub-types of hedges

Hyland (2005b), who provides the framework for this study, studies hedges as a homogenous kind or stance marker. In other words, Hyland (2005b) does not separate hedges into further sub-types. While analysing the corpus of ERC funded projects' summaries, it was noticed that not all hedges work simply by lowering the author's commitment to the proposition. Therefore,

to analyse hedges in more depth, the main types of hedges, called shields and approximators, were chosen, as described by Prince et al. (1980). Shields are a type of hedge which "affect the degree and type of speaker-commitment" (Prince et al. 1980:20) by expressing the writer's uncertainty towards the proposition using words such as *may*, *appear* or *possible*. Approximators "refer to the expressions which change the original meaning of a proposition or provide alternative meaning to the proposition" (Sayah and Hashemi 2014:594) and they often appeared as words such as *relatively*, *largely* or *potentially*. In other words, approximators alter the proposition itself by making it fuzzier, or less definite. The list of shields and approximators is provided in appendix 4.

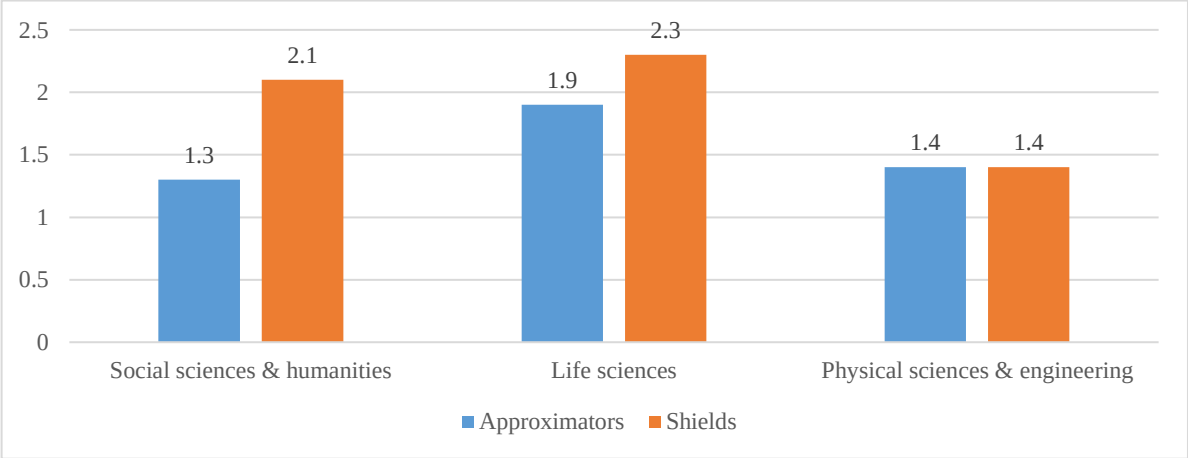

Figure 5. Sub-types of hedges by science field (occurrences per 1000 words)

Overall, shields occurred more frequently than approximators but the difference was not found to be statistically significant according to log-likelihood test. As seen in figure 5, in social sciences & humanities and life sciences, the frequency of occurrence of approximators was lower than the frequency of occurrence of shields. This might indicate that in those fields, commenting on the author's commitment to a proposition is more important than for physical sciences & engineering. Social sciences & humanities are traditionally a softer field, where not all facts are as definite as they might be in harder fields as they rely more on the author's interpretations. Writers might be expected to present their opinions more carefully, using more shields to remain as objective as possible. This effect is illustrated by example (12), where the writer lowers their own commitment to the proposition. As an example of a shield, *may* shows that the writer is careful and not willing to fully commit to a proposition which they might not have found definitive proof for.

(12) *Inequality **may** have been present throughout European prehistory, but manifest situationally through differential life chances, kinship, ritual or ancestorhood, rather than overtly through political command, wealth or identity. (SH-12)*

In contrast the frequency of occurrence of approximators was equal to the frequency of occurrence of shields in physical sciences & engineering. This shows that in this field, as opposed to the other two, it might be slightly more important to provide the information in a less definite form but at the fact's expense, rather than the writer's. This effect can be seen in example (13), where the writer provides alternative meanings to *the form* or *relapse* that the *patients* face.

(13) Yet, over the course of the following months or years, around 40% of the patients that underwent resection of the primary tumor with curative intention will relapse, ***generally*** *in the form of metastatic disease. (LS-24)*

It means that by removing the approximator *generally*, the writer would limit the forms of *relapse* to *only metastatic* disease but by using the approximators, it is signalled that there other forms of *relapse*. By not limiting the forms of *relapse*, the writer remains precise because there are other forms but only one form, which is mentioned, is relevant for the study. Therefore, approximators, as illustrated in example (13), do not lower the writer's commitment to the proposition but rather simply approximate, or round off, the data provided in the proposition.

3.3. Distribution of engagement markers between science fields

In this section, different engagement markers' distribution across the three sub-corpora will be analysed. Once again, I will begin with the most frequently occurred engagement markers and then move on to the ones that occurred less frequently. As shown in table 4, there were two types of engagement markers that did not occur and they will be discussed last. It is also important to note that as was pointed out earlier, engagement markers occurred far less frequently compared to stance markers. Due to the low frequency of occurrence and the fact that distinct sub-types of engagement markers were not clearly present in the corpus of ERC funded projects' summaries, sub-types of markers will not be discussed in this section as they were in the previous one.

Table 4. Engagement markers by science field (occurrences per 1000 words)

Stance marker	Social sciences & humanities	Life sciences	Physical sciences & engineering	Total
Reader pronouns	3.2	1.6	2.0	2.2
Questions	2.9	0.7	0	1.2
Appeals to shared knowledge	0.2	0.2	0	0.2
Personal asides	0	0	0	0
Directives	0	0	0	0

3.3.1. Reader pronouns

To start, the function of reader pronouns is described as a way of suggesting that the reader is "a member of the same discipline" (Hyland 2008:10), therefore bringing them closer into the discussion. Reader pronouns were the main way of creating the reader's presence in the summaries analysed. Results were rather different in a study carried out by Luan and Zhang (2018), who found that reader pronouns were among the least frequently used engagement markers in linguistic research articles. Yet, in the summaries analysed in this paper, reader pronouns were the most frequently used engagement marker, showing that perhaps using of words such as *we, us* and *our* to attain reader engagement was enough for the genre of ERC funded projects' summaries which are short texts.

In the corpus of ERC funded projects' summaries, reader pronouns were used to include the reader either as a member of the discipline or simply as a member of the human race. This is illustrated in example (14) where the writer uses *we* to include the reader into the discourse simply as a human being. The statement becomes relevant to the reader because the *ways that uniquely challenge how we live in relation to others* are applicable to the reader as a member of the same society.

*(14) Rapid advancements in machine learning technologies are transforming social and political life in ways that uniquely challenge how **we** live in relation to others. (SH-21)*

Moving on to the distribution among science fields in the corpus, reader pronouns occurred most frequently in social sciences & humanities. The difference of use of reader pronouns between science fields was found to be significant. According to log-likelihood test, social sciences & humanities had significantly more reader pronouns than other science fields. Thus, it can be said that social sciences & humanities find bringing the reader into the discourse more

significant. This goes in concert with the finding mentioned in the previous part, where writers for social sciences & humanities were found to use fewer self-mention markers, not making themselves stand out as much. Drawing these two facts together, it seems that social sciences & humanities indeed focus more not on the individual's but on the whole community's input into the scientific research.

3.3.2. Questions

The engagement marker to be discussed in this section is questions. They add a dialogic dimension to the text, helping the writer lead the reader through their speculations. As a second most frequently occurred engagement marker, questions seem to have an effect, which is at least sometimes sought after by the writers of ERC funded projects' summaries. Hyland (2005b) found that 80 per cent of the questions identified in the analysis were rhetorical questions, which worked to present the writer's opinion. The situation was different in the corpus of this study as all of the questions either presented the main problem that the project deals with or presented specific research questions as illustrated in example (15).

(15) *Our overarching research question –* ***What is the role of transport infrastructures in sustaining arctic communities?*** *(SH-24)*

Shifting the focus onto the distribution of questions among science fields, log-likelihood test showed that there were significant differences of use between all three scientific fields. As can be seen in table 4, questions did not occur in physical sciences & engineering sub-corpus. McGrath and Kuteeva (2011) found Similar results, they did not identify a single question in pure mathematics research articles. Thus, it seems that the traditionally more hard sciences do not use questions to create a dialogue with the reader. Questions did occur, though, in life sciences and social sciences & humanities sub-corpora. Similar to reader pronouns, questions include the reader into the discourse. Unlike reader pronouns, which simply create the presence of the reader, questions engage the reader in a dialogue that is happening within the text locally. Writers use them to communicate what the main problems and aims of the research described are. Hence, it can be said that the fields of life sciences and social sciences & humanities find the act of including their reader and even guiding them through what is discussed more important. This act, as mentioned already, is most important in social sciences & humanities, showing that this field, with the use of engagement markers, tends to focus more on their reader than the field of physical sciences & engineering.

3.3.3. Appeals to shared knowledge

Writers use appeals to shared knowledge to signal that a fact provided should be either agreed upon by the reader or at least familiar to them. As shown in table 4, these markers occurred only a handful of times across the whole corpus. They were found in social sciences & humanities and life sciences sub-corpora only. They did not occur in physical sciences & engineering sub-corpus. The difference between the aforementioned frequencies, according to log-likelihood test, was found to be insignificant. That shows that, in the whole corpus of this study in general, appeals to shared knowledge were an insignificant feature. Other studies, however, found appeals to shared knowledge to occur more frequently. They were found to be among the more frequent engagement markers by Luan and Zhang (2018) and Keramati et al. (2019), in their studies of linguistics related research articles. That might show, that writers could be more keen on using appeals to shared knowledge in lengthier texts. However, in summaries of ERC funded projects, the effect of signalling that a fact should be familiar or agreed upon by the reader is unnecessary.

3.3.4. Personal asides and directives

Both personal asides and directives, as shown in table 4, did not occur in the corpus of ERC funded projects' summaries and therefore cannot be discussed more in-depth. Perhaps, the only aspect that could be commented upon is that these two markers, as engagement markers, did not occur in summaries or ERC funded projects because the genre of summary would hardly allow them to. In other words, it is hard to even imagine summaries to use personal asides, which halt the flow of the text to offer a writer's personal comment. The same can be said about directives, which can instruct the reader to stop and think about something, to look at some other piece of information, like a chart or a different page, or even to perform a certain physical action. Thus, in this case, it is the genre of summary which simply finds personal asides and directives unnecessary, regardless of the science field.

4. Conclusions

In this paper, the following research questions were raised: Do European Research Council funded projects' summaries use more stance or engagement markers? How are different stance and engagement markers used in summaries of ERC funded projects written for different fields of science? What sub-types of stance and engagement markers are used in summaries of ERC funded projects and how do they describe the different science fields?

To answer the first research question, ERC funded projects' summaries used ten times more stance markers than engagement markers. This shows that writers of the analysed texts found building their authorial persona and standing out as competent researchers much more important than engaging their reader and leading them through the text. This is hardly surprising due to the length of summaries, which allows only the most essential information to be included.

To answer the second research question, significant difference was found between the use of stance and engagement markers in social sciences & humanities, life sciences and physical sciences & engineering. The use of attitude markers showed that life sciences and physical sciences & engineering found expressing the writer's affective attitude more important. That may signal that it is more important to stand out as individual or teams of scientists in those fields. The marker frequency distribution of self-mention markers showed that in life sciences it was much more important to indicate the presence of the author as an important figure. That could mean that life sciences as a field rely more on research teams and less on the scientific community as a whole. In a similar way, the use of reader pronouns revealed that social sciences & humanities address the presence of the reader, which in turn suggests that more focus is put onto the scientific community. Lastly, the use of questions also suggested that texts in social sciences & humanities have a heavier focus on the reader, guiding them through the text, making sure that the reader is on the same level as the writer.

To answer the last question, different types were identified for stance markers but not engagement markers as they occurred much less frequently. For attitude markers, four specific sub-types and one unspecific sub-type were identified and it was found that writers used attitude markers mostly to refer to the importance, novelty, uniqueness and clarity of the methods, problems and aims described. Self-mention markers were separated into two types, ones that refer to a single person and ones that refer to multiple people. Among all three scientific fields, self-mention markers were sometimes used to refer to writers as individuals but significantly more self-mention markers referred to several people, or simply to the team of researchers who are proposing the project. This suggests that ERC funded projects often rely on a whole team of researchers to carry out research. Boosters were found to only occur as adverbs and

adjectives. It was observed that boosters occurred in the shape of adverbs more often than in the shape of adjectives. For hedges, sub-types called shields and approximators, as defined by Prince (1980), were found. Social sciences & humanities and life sciences were found to use more shields, signalling the writer's lower commitment to the proposition in order not to make sweeping generalisations. Physical sciences & engineering were found to use approximators as frequently as shields, showing that, comparatively, they tend to simplify the facts provided in the text.

Because of the limitations of form and time, a relatively small corpus was compiled. Also, the statistical analysis that was carried out was uncomplicated and did not require deeper knowledge in the field of statistics as well as more intricate statistical analysis software. For further research of stance and engagement markers in ERC funded projects' summaries, I would suggest a larger data sample as well as a deeper statistical analysis, for example, using chi squared test, which might help in carrying out a deeper analysis of the data and in learning more about the interesting genre of ERC funded projects' summaries.

Summary in Lithuanian

Šiame darbe yra analizuojami atskirų mokslo sričių tekstų skirtumai tyrimų paraiškų santraukose. Lyginamąjai, tekstynais paremtai kiekybinę ir kokybinę analizei atlikti, buvo pasitelkta metodologinė prieiga, kurią aprašė Hyland (2005b). Ja buvo tiriama autoriaus pozicijos raiška ir santykio su skaitytoju kūrimas Europos mokslo tarybos finansuojamų projektų santraukose. Analizėje lyginimui buvo pasirinktos socialinių ir humanitarinių mokslų, gyvybės mokslų ir fizikos mokslų bei inžinerijos sritys. Iš minėtų mokslo sričių projektų santraukų, lygiomis dalimis buvo sukurtas tekstynas, kurį sudarė viso 90 tekstų. Kiekvienas tekstas buvo analizuojamas be kompiuterinių programų pagalbos. Tyrimo rezultatai parodė, kad analizuotuose tekstuose, autoriaus pozicijos raiška buvo pasitelkiama gerokai dažniau, negu santykio su skaitytoju kūrimo būdai. Vis dėlto, lyginant mokslo sritis, gyvybės moksluose ir fizikos moksluose bei inžinerijoje buvo atrasta daugiau autoriaus pozicijos raiškos, negu jos buvo atrasta socialiniuose ir humanitariniuose moksluose. Tai parodė, kad gyvybės mokslų ir fizikos mokslų bei inžinerijos autoriai daugiau dėmesio teikė savęs, kaip autoriaus, išryškinimui. Taip pat, buvo atrasta, kad socialinių ir humanitarinių mokslų autoriai pasitekldavo santykio su skaitytoju kūrimo būdus dažniau negu kitų mokslo sričių autoriai. Dėl to, manoma, kad socialinių ir humanitarinių mokslų autoriai yra truputį labiau orientuoti į skaitytoją, labiau įtraukdami jį į diskursą tam, kad aiškiau pristatytų savo projektus.

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Appendix 1. Sub-types of attitude markers

Sub-type	Social sciences & humanities	Life sciences	Physical sciences & engineering
Uniqueness	First-time: 4 State-of-the-art: 3 Uniquely: 2 Distinct: 1 Distinctive: 1 Phenomenal: 1 Radical: 1 Surprising: 1 Unique: 1 Unparalleled: 1 Unprecedented: 1 Unrivalled: 1	Unique: 10 Pioneering: 2 Breakthrough: 1 Cutting-edge: 1 Surprisingly: 1 The first: 1 Unconventional: 1 Unprecedented: 1	First time: 8 Unique: 8 Unprecedented: 4 Revolutionary: 2 Unveil: 2 Breakthrough: 1 Breakthroughs: 1 Cutting-edge: 1 Extraordinary: 1 Frontier: 1 Has never been: 1 Non-conventional: 1 Revolutionize: 1 State-of-the-art: 1 The first: 1 Uniquely: 1 Unrecognized: 1 Unrivalled: 1
Novelty	New: 10 Novel: 7 Innovative: 3 Innovation: 1 Timely: 1	Novel: 24 New: 23 Recently: 8 Recent: 4 Innovative: 2 Current: 1 Timely: 1	New: 37 Novel: 9 Emergent: 3 Recently: 3 Recent: 2 Current: 1 Currently: 1 Innovative: 1
Importance	Fundamental: 4 Ground-breaking: 4 Important: 2 Key: 2 Major: 2 Profound: 2 Capstone: 1 Critical: 1 Crucial: 1 Importantly: 1 Integral: 1 Pivotal: 1 Pressing: 1 Relevant: 1 Remarkable: 1 Significance: 1 Significant: 1 Urgent: 1 Valuable: 1	Major: 9 Fundamental: 7 Key: 6 Ground-breaking: 6 Essential: 4 Crucial: 3 Critical: 2 Crucially: 2 Hallmark: 2 Dominating: 1 Importance: 1 Important: 1 Importantly: 1 Indispensable: 1 Necessity: 1 Pivotal: 1 Primary: 1 Remarkable: 1 Remarkably: 1	Fundamental: 12 Key: 12 Important: 6 Major: 5 Significant: 3 Cornerstone: 2 Essential: 2 Ground-breaking: 2 Main: 2 Outstanding: 2 Remarkable: 2 Serious: 2 Urgently: 2 Core: 1 Crucial: 1 Dearly: 1 Desirable: 1 Great: 1 Importance: 1 Instrumental: 1

	Vital: 1	Significant: 1	Invaluable: 1 Necessary: 1 Necessitate: 1 Pillars: 1 Precious: 1 Primary: 1 Relevant: 1 Required: 1 Ultimate: 1 Underlying: 1
Clarity	Comprehensive: 3 Grounded: 2 Nuanced: 2 Sound: 2 Clearer: 1 Consistently: 1 Deep: 1 Deepening: 1 Enigmatic: 1 Improved: 1 Intensively: 1 Loosely: 1 Paradoxically: 1 Precisely: 1 Problematic: 1 Understudied: 1 Well-founded: 1	Comprehensive: 3 Unclear: 3 Elusive: 2 Hampered: 2 Complexity: 1 Deeper: 1 Deeply: 1 Full: 1 Ill-defined: 1 Undefined: 1 Understudied: 1 Unexplored: 1 Uninvestigated: 1 Unknown: 1 Well-defined: 1 Well-known: 1	Complicated: 1 Deeper: 1 Neglected: 1 Rational: 1 Rationally: 1 Simpler: 1 Straightforward: 1 Uncertainty: 1 Unexplored: 1 Well-defined: 1 Well-founded: 1
Other	Acrimonious: 1 Ambitious: 1 Artificially: 1 Differentially: 1 Disappointing: 1 Dynamic: 1 Enormous: 1 Excessive: 1 Exciting: 1 Impressive: 1 Interesting: 1 Lack: 1 Lasting: 1 Rapid: 1 Strong: 1 The best: 1 Uncomfortable: 1 Universal: 1 Violent: 1	Affordable: 2 Eventually: 2 Extensive: 2 Advanced: 1 Daunting: 1 Devastating: 1 Difficult: 1 Effectively: 1 Efficacious: 1 Efficacy: 1 Far-reaching: 1 Good: 1 High risk/high gain: 1 Ideal: 1 Impeding: 1 Integrated: 1 Interestingly: 1 Intricately: 1 Long-lasting: 1 Natural: 1	Promising: 3 Ambitious: 2 Inexpensive: 2 Longstanding: 2 Reliable: 2 Better: 1 Challenging: 1 Devastating: 1 Easily: 1 Efficient: 1 Excellent: 1 Improved: 1 Inaccessible: 1 Interesting: 1 Invigorated: 1 Obstacle: 1 Poor: 1 Potential: 1 Problematic: 1 Rapidly: 1 Responsible: 1 Rigorous: 1

		Neglected: 1 Overwhelming: 1 Poor: 1 Realistic: 1 Safety: 1 Saturated: 1 Striking: 1 Sufficiency: 1 Sufficient: 1 Underestimated: 1 Underlying: 1 Unexpected: 1 Useful: 1 Versatile: 1 Well-curated: 1	Robust: 1 Seamless: 1 Sophisticated: 1 Successfully: 1 Surprisingly: 1 Sustainable: 1 Traditionally: 1 Untapped: 1

Appendix 2. Sub-types of self-mention markers

Sub-type	Social sciences & humanities	Life sciences	Physical sciences & engineering
Referring to a single person	I: 6 Me: 1 My: 1	I: 23 My: 13	I: 12 My: 3
Referring to multiple people	We: 11 Our: 7 Us: 1	We: 80 Our: 19 Us: 1	We: 24 Our: 12

Appendix 3. Sub-types of boosters

Sub-type	Social sciences & humanities	Life sciences	Physical sciences & engineering
Adverbs	Fundamentally: 3 Greatly: 3 Significantly: 2 Always: 1 Completely: 1 Definitely: 1 Entirely: 1 Extremely: 1 Highly: 1 Increasingly: 1 Inevitably: 1 Intimately: 1 Much: 1 Particularly: 1 Profoundly: 1 Radically: 1 Strongly: 1 Well: 1	Highly: 3 Completely: 2 Very: 2 Definitely: 1 Dramatically: 1 Extensively: 1 Greatly: 1 Much: 1 Only: 1 Prohibitively: 1 Remarkably: 1 Significantly: 1 Tightly: 1 Tremendously: 1 Widely: 1	Highly: 7 Dramatically: 6 Strongly: 3 Very: 3 Completely: 2 Greatly: 2 Extremely: 1 Fundamentally: 1 Much: 1 The most: 1

Adjectives	Substantial 1 Tremendous 1	Great: 3 Major: 3 Vast: 2 Confident: 1 Extensive: 1 Extraordinary: 1 Large: 1 Strong: 1 The best: 1	Huge: 2 Big: 1 Complete: 1 Dramatic: 1 Enormous: 1 Extensive: 1 Full: 1 High: 1 Profound: 1 Rapid: 1 Vast: 1
Sub-type	Social sciences & humanities	Life sciences	Physical sciences & engineering

Appendix 4. Sub-types of hedges

Sub-type	Social sciences & humanities	Life sciences	Physical sciences & engineering
Approximators	Relatively: 2 Largely: 3 Generally: 1 Often: 1 Potentially: 1 Primarily: 1	Most: 4 Largely: 3 Likely: 2 Mostly: 2 About: 1 Commonly: 1 Generally: 1 Often: 1 Rather: 1	Potentially: 3 Largely: 2 Most: 1 Mostly: 1 Much: 1 Rather: 1 Relatively: 1 Typically: 1 Virtually: 1
Shields	May: 3 Appear(s): 2 Argue(s): 2 Could: 2 Would: 2 Arguably: 1 Better: 1 Claim: 1 Hypothesis: 1 Hypothesize: 1 Perhaps: 1 Possibility: 1	May: 7 Could: 2 Expect: 2 Possible: 2 Hypothesize: 1 If successful: 1 Possibly: 1 Propose: 1 Should: 1 Suggest: 1 Would: 1	Could: 4 Would: 3 Possible: 2 Expected to: 1 If successful: 1 Might: 1

Appendix 5. The corpus of ERC funded projects' summaries

All stance and engagement markers identified were colour-coded as follows:

Hedges – light blue

Boosters – dark blue

Attitude markers – bright green

Self-mention – dark green

Reader pronouns - yellow

Questions - olive

Appeals to shared knowledge – purple

The corpus compiled for this paper, as it was analysed, is provided in three parts for the three sub-corpora below.

Social sciences & humanities (SH) sub-corpus

SH-1. Becoming a mother: An integrative model of adaptations for motherhood during pregnancy and the postpartum period.

Pregnancy involves biological adaptations that are necessary for the onset, maintenance and regulation of maternal behavior. We were the first group to find (1, 2) that pregnancy is associated with consistent, pronounced and long-lasting reductions in cerebral gray matter (GM) volume in areas of the social-cognition network. The aim of BEMOTHER is to develop an integrative model of the adaptations for motherhood that occur during pregnancy and the postpartum period by: i) establishing when the brain of pregnant women begins to change and how it evolves; ii) characterizing the dynamics of cognitive performance, theory-of-mind, maternal-infant bonding and psychiatric measures; iii) assessing the effect of environmental and/or psychological factors in the maternal adaptations, iv) identifying the metabolomics biomarkers associated with maternal adaptations, and v) integrating the previous findings within the Research Domain Criteria framework (RDoC) (3). We will use a prospective longitudinal design at 5 time points (1 pre-pregnancy session, 2 intra-pregnancy sessions and 2 postpartum sessions) during which neuroimaging, psychological, behavioral and metabolomics data will be acquired in 3 groups of women: a group of nulliparous women who will be undergoing a full-term pregnancy, another group of nulliparous women whose same-sex partners will undergo a full-term pregnancy, and a group of control nulliparous women. We

will provide the longitudinal RDoC-based model at the end of the study, but we will also deliver intermediate longitudinal evaluations after the postpartum session, as well as cross-sectional analyses after the first intra-pregnancy session and the postpartum session. BEMOTHER is timely and innovative. It adopts the translational RDoC framework in order to provide a pioneering, comprehensive and dynamic characterization of the adaptations for motherhood, addressing the interaction among different functional domains at different levels of analysis.

SH-2. An object-oriented approach to color

There have been tremendous advances in color science. The absorption of photons by three types of photoreceptors is known at the molecular genetic level. Human cone fundamentals are tabled to several decimal places and color opponency is understood at the neural and computational level. Yet, all this knowledge is based on extremely restrictive assumptions with a colored light in the dark (Color 1.0) or flat, matte surfaces in a uniformly colored context (Color 2.0). But which mechanisms mediate perception of colors in the real world– when looking at a field of flowers or searching for a certain product in the supermarket? Arguably, the most important function of color is the processing of information about objects in scenes. It is the tight link to objects through which color helps us see things quicker and remember them better. This proposal, Color 3.0, is based on an active observer dealing with three-dimensional objects in natural environments. It deals with the dimensions relevant for the main purpose of color perception – intensity, hue and saturation. The goal is to fundamentally rethink color science around real world objects and natural tasks. We will gain a deep understanding of the circuitry underlying color perception in real and virtual worlds, a Deep Neural Network model of color processing that can be traced through the brain, a new colorimetry based on natural object colors rather than flat, matte patches of light, and last but not least a better measure for luminous intensity that can deal with objects of different color. This could lead to a revision of how we study the early visual system, better color reproduction and better lighting systems. Our use of real-time raytracing in VR could cause a paradigm shift in vision science, away from a passively viewing observer pushing buttons, towards an active observer situated in a virtual world and performing a natural task.

SH-3. Material Constraints Enabling Human Cognition

Recent breakthroughs in comparative neurobiological research highlight specific features of the connectivity structure of the human brain, which open new perspectives on understanding the

neural mechanisms of human-specific higher cognition and language. In delineating the material basis of human cognition and language, neurobiologically founded modelling appears as the method of choice, as it allows not only for 'external fitting' of models to key experimental data, but, in addition, for 'internal' or 'material fitting' of the model components to the structure of brains, cortical areas and neuronal circuits. This novel research pathway offers biologically well-founded and computationally precise perspectives on addressing exciting hitherto unanswered fundamental questions: How can humans build vocabularies of tens and hundreds of thousands of words, whereas our closest evolutionary relatives typically use below 100? How is semantic meaning implemented for gestures and words, and, more specifically, for referential and categorical terms? How can grounding and interpretability of abstract symbols be anchored biologically? Which features of connectivity between nerve cells are crucial for the formation of discrete representations and categorical combination? Would modelling of cognitive functions using brain-constrained networks allow for better predictions on brain activity indexing the processing of signs and their meaning? This project will use novel insights from human neurobiology translated into mathematically exact computational models to find new answers to long-standing questions in cognitive science, linguistics and philosophy. Models replicating structural differences between human and non-human primate brains will help delineate mechanisms underlying specifically human cognitive capacities. Key experiments will validate critical model predictions and new neurophysiological data will be applied to further improve the biologically-constrained networks.

SH-4. Psychobiological mechanisms of pain persistence

Persistent or chronic pain is a key medical and societal problem. In the last decades, biomedical research has undertaken enormous efforts to develop treatments for persistent pain, but the results have been disappointing. This project proposes a radical shift, namely to target the early development of pain persistence and to investigate psychological interventions directed at negative expectations, control and reward in experimental long-term pain studies. A methodological work package will develop novel tools, such as MR spectroscopy of the spinal cord, to track metabolic changes related to persistent pain, and to identify the mechanisms of the proposed interventions. All studies are guided by an integrative model outlining how psychological factors, such as negative expectations and loss of control, can affect the development of pain persistence, and more importantly, how to counteract this process. We will, for example, augment the perception of pain decreases by expectations or use reward manipulations to reinstantiate the effectiveness of the pain modulatory system. Finally, the

model proposes that the inability to control pain leads to a state of helplessness. Consequently, the role of helplessness will be investigated and we will test interventions with the goal to allow subjects to regain control over their pain. This will be possible, through the development of a novel pain assessment device, which can be used to detect spontaneous pain decreases and prompt the subject to perform an action (i.e. self-administer a putative treatment). Through the illusion of control, subjects perceive that their action is causal for the pain relief, even though it is actually pain reductions that trigger their action. In the future, this will also allow treatment of patients in which pain is already persistent, and allow them to regain perceived control over, and hence reduce, their pain.

SH-5. The dynamics of sign language grammar: Morphology, language change, iconicity, and social structure in signing communities

SignMorph aims to address two of the most fundamental questions in the language sciences: how much do the languages of the world resemble each other and how do they differ, and what factors account for both the cross-linguistic similarities and the differences? SignMorph will provide answers to these questions about the nature of human language through a focus on the sign languages of deaf communities. This project will also be the first to focus on key aspects of the grammar across three distinct subtypes of signing communities: (1) established macro-community sign languages used across an entire national deaf community, (2) established micro-community sign languages which are languages in smaller communities within a nation state, and (3) emerging sign languages which are sign languages that have only begun to emerge in the late 20th century. The driving research question is: sign languages are natural languages, but what kind of languages are they? SignMorph aims to better understand similarities and differences in the grammar of sign languages, and how these are shaped by language-internal and language-external factors. The factors to be investigated in the study include (1) the role of iconicity in mapping grammatical meanings onto form, (2) the relatively recent emergence of sign languages, and how their short history has impacted on the processes which create grammatical structure, and (3) the sociolinguistic structure of signing communities, particular the effect of the large proportion of child to child (rather than parent to child) transmission of sign languages, varying ages of first language acquisition, and variation in interaction individuals have with native signers through their social networks. The study of this distinctive combination of characteristics in sign languages means that this project will make a vital contribution to an understanding the human language capacity more generally.

SH-6. Sleep balancing abstraction and forgetting of memory

Sleep supports the formation of long-term memory, a function described as an active systems consolidation process. Concurrently, a long tradition of theorizing exists that sleep serves to forget unimportant memory. Paradoxically, the crucial behavioral demonstration that sleep induces forgetting is currently entirely missing. I hypothesize that memory processing during sleep is balanced: Sleep consolidates abstracted schema-like memory and this process is coupled to active forgetting of episodic detail. This twofold function of sleep is most prominently expressed, with a time delay, after learning large amounts of information exhausting the limited capacities of memory processing during sleep. It is particularly pronounced during development when due to a lack of preexisting knowledge, the brain faces conditions of permanent information overload. I will combine human and rodent studies to test the behavioral predictions of this hypothesis and to characterize the underlying neural mechanisms. Adopting the active systems consolidation framework, I target the following aims: 1) to provide direct behavioral evidence that with high information load, sleep compared to wakefulness induces forgetting of episodic detail in favor of consolidating abstracted schema-like memory. 2) to clarify how memory abstraction and forgetting are linked to slow wave sleep (SWS) and REM sleep, their characteristic EEG oscillations, and underlying forming and pruning of synapses. Specifically, I hypothesize that spindles support memory abstraction whereas slow oscillations, hippocampal ripples and REM theta concurrently contribute to both memory abstraction and forgetting. 3) to demonstrate enhanced sleep-dependent memory abstraction and forgetting during early development. This project by providing first-time systematic evidence that and how sleep transforms memory to induce forgetting, will greatly advance our understanding of sleep's memory function and its multiple applications.

SH-7. Neural origins of mind reading

Human thoughts have no mass and remain definitely hidden from others' view. Still, we are remarkable at predicting others' mental states from observable phenomena. Sensitivity to eye cues enables us, for example, to detect the presence of other minds, assess theirs content and interact with them through eye contact, gaze following and joint attention. Emerging in early infancy, these competences are precursor to later mentalizing abilities and are known to depend upon a set of cerebral structures overlapping with the theory of mind network, under the regulatory influence of neuropeptides such as oxytocin. While the existence of theory of mind

in monkeys and apes is a matter of debate, these animals attend to eyes and understand what others see. Non-human primates thus offer a valuable perspective on the evolutionary path that shaped our brain to use eyes as a social interaction device and as a window into other's mind. SOCIALEYES will aim to test the hypothesis that "eye reading" is rooted in conserved visual specializations, shared with functions like threat and danger detection. It will emphasize the role of a subcortical network that includes the hypothalamic oxytocin system, superior colliculus and amygdala. The links between eye processing, joint attention and knowledge states attribution (WP1) will be investigated in socially-interacting monkey dyads. The contribution of the colliculus and amygdala to joint attention mechanisms will be compared to that of core mentalizing regions of the cortex (WP2) using single neuron recordings. The functional role of oxytocin signaling within this network on joint attention and eye reading behavior (WP3) will be evaluated with site- and cell type-specific reversible inactivation procedures. Finally, the relevance of joint attention and eye reading abilities to natural social interactions (WP4) will be tested using novel ethological and computer vision-based behavior recognition methods in freely behaving monkeys.

SH-8. Cross-Linguistic statistical inference using hierarchical Bayesian models

Historical linguistics and linguistic typology share the objective of explaining cross-linguistic variation. Their traditional research agendas have been largely disjoint though since historical linguistics strives for depth and typology for breadth. This tension has been replicated in current statistical and computational renderings of two sub-disciplines. Computational models of language change generally focus on individual language families, while statistical typology pays little attention to diachronic processes. CrossLingference will bridge this gap. Using Bayesian hierarchical models, the reach of modern phylogenetic linguistics will be extended to cross-family models, where each lineage is assumed to follow its own dynamics, but cross-family variation is constrained and data from one family are used to make inference about the processes in other families. At the same time, state-of-the-art generalized linear mixed models will be extended to control both for genealogical history and language contact. These model-based approaches will be complemented by agent-based simulations. CrossLingference will implement this general programme for the following domains of application, securing a lasting impact both on statistical typology and on computational historical linguistics: - Sound laws in language change, enabling automatic reconstruction of proto-language vocabulary, - Causal relationships between typological variables. - Factoring of universal tendencies, historical

contingencies and language contact in explaining variation in word-order types and inflectional paradigms.

SH-9. Genetically Evolving Models of Science

The development of scientific models suffers from two related problems: ever-growing number of experimental results and scientists' cognitive limitations (including cognitive biases). This multidisciplinary project (psychology, computer modelling, computer science and cognitive neuroscience) addresses these problems by developing a novel methodology for generating scientific models automatically. The methodology is general and can be applied to any science where experimental data are available. The method treats models as computer programs and evolves a population of models using genetic programming. The extent to which the models fit the empirical data is used as a fitness function. The best models–potentially modified by cross-over and mutation–are selected for the next generation. Pilot simulations have established the validity of the methodology with simple experiments. To demonstrate that the methodology is sound, can be used with complex datasets and can be generalised across sciences, four related strands of research are planned. First, 'Building New Tools' develops the methodology and creates techniques to understand and compare the evolved models. Second, 'Explaining Human Data' uses the methodology to explain a wide range of data on human cognition. This will be done in two steps: (a) data without learning (working memory and attention); and (b) data with learning (categorisation, implicit learning and explicit learning). Third, 'Explaining Animal Data' develops models to account for various aspects of animal behaviour, focusing on conditioning and categorisation. Finally, 'Explaining Neuroscience Data' extends the methodology to account for data combining information about cognitive and brain processes. This project explores virgin territory and thus opens up a new field of research. It combines insights from experimental psychology, cognitive modelling, cognitive neuroscience and computer science, disciplines in which the PI has strong track record.

SH-10. Spatio-temporal mechanisms of generative perception

How do we rapidly and effortlessly compute a vivid veridical representation of the external world from the noisy and ambiguous input supplied by our sensors? One possibility is that the brain does not process all incoming sensory information anew, but actively generates a model

of the world from past experience, and uses current sensory data to update that model. This classic idea has been well formulised within the modern framework of Generative Bayesian Inference. However, despite these recent theoretical and empirical advances, there is no definitive proof that generative mechanisms prevail in perception, and fundamental questions remain. The ambitious aim of GenPercept is to establish the importance of generative processes in perception, characterise quantitatively their functional role, and describe their underlying neural mechanisms. With innovative psychophysical and pupillometry techniques, it will show how past perceptual experience is exploited to manage and mould sensory analysis of the present. With ultra-high field imaging, it will identify the underlying neural mechanisms in early sensory cortex. With EEG and custom psychophysics it will show how generative predictive mechanisms mediate perceptual continuity at the time of saccadic eye movements, and explore the innovative idea that neural oscillations reflect reverberations in the propagation of generative prediction and error signals. Finally, it will look at individual differences, particularly in autistic perception, where generative mechanisms show interesting atypicalities. A full understanding of generative processes will lead to fundamental insights in understanding how we perceive and interact with the world, and how past perceptual experience influences what we perceive. The project is also of clinical relevance, as these systems are prone to dysfunction in several neuro-behavioural conditions, including autism spectrum disorder.

SH-11. African Abolitionism: The Rise and Transformations of Anti-Slavery in Africa

The historiography of Euro-American abolitionism is so vast that it has a history of its own (Brown 2006). By contrast, research on African abolitionism is a narrow field focused primarily on European anti-slavery activities. It presupposes that when Europe abolished slavery in Africa, Africans became abolitionists. This conclusion is unfounded. Many general questions have never been asked: When and where did African abolitionist movements develop? Who are the main ideologues of African abolitionism? How did abolitionism spread, among which groups? What forms of political struggle did African anti-slavery give rise to? While individual African abolitionists and regional movements have attracted limited attention, there is no major review of the phenomenon on a continental scale. AFRAB fills this gap. It contributes to African and global history and slavery studies by analyzing and comparing African abolitionist ideas and anti-slavery movements, the long-term consequences of European abolitionism, and the resilience of pro-slavery discourses.

SH-12. Making Ancestors: The Politics of Death in Prehistoric Europe

How did politics and inequality work in prehistoric Europe? Traditionally, politics has been seen in terms of discrete political ranks identified through differential treatment of individual burials. But this results in classifying much of prehistory, where the dead were treated in ways which effaced individual identity, as egalitarian. The result is an artificially dichotomous history: Neolithic people had landscapes, rituals and ancestors, Bronze and Iron Age people had politics and inequality. In the last two decades this approach has been strongly critiqued. Burial treatment rarely relates to status so directly; the dead serve many different political roles. Inequality in pre-state groups rarely consists of clear strata; inequality and equality exist in tension within groups. Inequality may have been present throughout European prehistory, but manifest situationally through differential life chances, kinship, ritual or ancestorhood, rather than overtly through political command, wealth or identity. But this new perspective has never been tested empirically. This project tests alternative models of prehistoric inequality and deathways. To investigate social relations in life, it uses osteobiography, reconstructing life stories from skeletons through scientific data on identity, health, diet, mobility and kinship. To understand deathways, it employs a second new methodology, funerary taphonomy. Combining osteobiography and taphonomy allows us to connect ancient lives and deaths. Peninsular Italy provides a substantial test sequence typical of much of Europe. For each of three key periods (Neolithic, 6000-4000 BC; Final Neolithic to Early Bronze Age, 4000-1800 BC; Middle Bronze Age to Iron Age, 1800-600 BC), 200+ individuals will be analysed. The results will allow us to evaluate for the first time how inequality affected lives in prehistoric Europe and what role ancestors played in it.

SH-13. 1,000 ancient genomes: gene-economy innovation in cattle, sheep and goat

The genetic threads of goat, cattle and sheep ancestry have been woven by human breeding, environmental pressures, hybridisation and the chance effects of genetic drift. The ancestral weaves of these key animals intertwine with human creativity in the most profoundly innovative episodes of the human past. Three broad episodes of particular import were: initial domestications circa 11 kya in Southwest Asia; the intensification circa 6 kya of use of those animal products which are harvested without killing such as wool, milk and traction; and the development of exceptionally productive landraces, later formalized into breeds, in recent millennia. However, each of these is loosely defined in time and space, the key traits are often osteologically invisible, and the vectors of causality in their virtuous cycles of gene-economy

innovation are completely unknown. A combination of high coverage ancient whole genome data coupled with new analysis methods that allow efficient computation of genomewide locus genealogies will be used to untangle the threads of ancestry in sheep, cattle and goat across the whole genome in these transformative phases. Combining these with additional low coverage genomes generated from less preserved samples will generate a total set of 1,000 ancient animal genomes. These data will be unprecedented and will allow tracking of selection at trait genes, in order to detect human agency in breeding and, in collaboration with archaeologist partners, asking are there periods and places where threads of innovation coalesce. The project will also use ancient epigenetics to explore archaeological variation in gene activation patterns and will seek to understand the problematic build up of harmful mutations that threaten livestock today. With cognate disciplines, it will compare signals of animal mobility identifying distinct genetic strata correlating with archaeological horizons and affording the prospect of DNA-dating in future excavation.

SH-14. Text, materiality, and multiculturalism at the crossroads of the ancient Mediterranean

'Crossreads' will offer the first coherent account of the interactions and interplay of linguistic and textual material culture in ancient Sicily over a period of 1,500 years. Sicily was a multilingual, multicultural region at the crossroads of the ancient Mediterranean, colonised and invaded repeatedly by Phoenicians, Greeks, and Romans. History has traditionally prioritised literary texts, creating a Helleno- and Romanocentric narrative, which often relegates the island to a footnote. However, the inhabitants, native and immigrant, did write and those texts survive, engraved on a variety of durable materials – the practice of epigraphy. These texts embrace a broad socio-economic range, across public and private life. Proceeding from an unparalleled unification and exploitation of all the texts from the island (7th cent. BCE – 7th cent. CE) in a single corpus, 'Crossreads' will combine the insights from the collected corpus with the insights and analysis resulting from three major subprojects. These will explore the historical linguistics of the texts, the social, economic and practical materiality of the stone texts, and the physical forms of the writing systems employed – and interactions between all these aspects. Building upon a successful pilot project (I.Sicily), 'Crossreads' will bring all these inscribed objects together for the first time in a comprehensive, open-source, digital corpus using international standards to encode text, images and contextual data. The project pioneers the use in ancient epigraphic studies of new digital tools in palaeography and linguistic annotation, and offers the first petrographic analysis of the use of stone on the island. No such analysis has been attempted on this scale nor across this range of material, and it promises unparalleled insights into the

cultural interactions at the heart of the Mediterranean, between Greek East and Latin West, North Africa, indigenous voices, and others.

SH-15. Twentieth-Century International Economic Thinking, and the Complex History of Globalization

Today globalization, the integration of the world's economies, is blamed for crises of corporate excess, gaping economic inequality and revived populist nationalisms; to understand its complex history is more pressing than ever. ECOINT advances an innovative approach to the study of the struggles over economic ideas that have fashioned the paths to globalization. It shifts our focus from international economic thought as an unanchored field of ideas, to 'international economic thinking', generated in and through institutional sites distinctive to the 20th century: intergovernmental organisations and associated international non-governmental organisations. ECOINT adds to the history of globalization important but understudied economic thinkers, namely mid-level and 'non-intellectual' intellectuals, many of them women, working with and in these organizations, from 1919 until 2001. Hence, ECOINT provides a nuanced history of twentieth century international economic thinking and imaginaries, while making a unique contribution to understanding of the international 20th century. Above and beyond, ECOINT will ask: What difference did women economic thinkers make in the course of globalization? And what was the role of business, operating through INGOs? Using largely neglected private and public archives, ECOINT will produce a capstone global history of international economic thinking, and social history of women economic thinkers in international institutions. It will capture the extent and breadth of international economic thinking at major IGOs— particularly the UN Regional Economic Commissions in Europe, Latin America, Asia and the Pacific, and Africa—and the INGOs the International Federation of Business and Professional Women and International Chamber of Commerce. Within five years, ECOINT will have mapped the range of international economic thinking, the impact of women and business in the complex history of globalization.

SH-16. Global Correspondent Banking 1870-2000

The overall objective of GloCoBank is to analyse the changing shape of international banking networks across the 20th century using an innovative methodology that allows greater specificity and inclusion than ever before. The bilateral correspondent banking network that will be uncovered by GloCoBank was the structure on which the global financial system was

built and on which the trade and specialization that drove global development was based, but we know very little about it. When merchants settled accounts across borders, they did so through transfers from the merchant's bank to the customer's bank. From the time of the telegraph in the late 19th century, the contraction of time and space was accomplished by sending telegraph messages from the buyer's home bank to an agent in the seller's country to transfer funds to the seller's bank. These interbank connections remain the underlying architecture of the global payments system but we do not have a complete sense of how they were built, managed or how they changed over time. Existing literature on global payments relies on official data on capital flows that are exclusively available at a national level which prevents an analysis by type of bank, sub-national region, or more specific location. Moreover, these national data on bank flows are also consistently available for most countries only from 1960, which truncates our ability to assess the changing geography of international banking during periods of upheaval such as wars, economic crisis or depression. To date there has been no comprehensive data source to accomplish this. GloCoBank will create and analyse a new set of data and combine it with extensive archival research, which will allow a much more granular assessment of the patterns and dynamics of international banking and payments. The data will capture the links between thousands of individual banks involved in international payments through bilateral correspondent banking contracts across 130 years.

SH-17. The Memory of Financial Crises: Financial Actors and Global Risk

This project explores the extent to which the memory, or absence of memory, of previous financial crises can explain practices threatening the stability of the financial system. This will provide a major contribution to the understanding of the causes of financial crises, in particular the Global Financial Crisis, by helping to understand the behaviour of financial agents, marked by recurrent waves of over-confidence and excessive risk-taking, and why regulators fail to maintain financial stability. The project addresses four main questions: How are financial crises remembered? Has the memory of financial crises had an impact on the thinking and behaviour of financial actors? Has a 'new' financial elite emerged in the late twentieth and early twenty-first century? What has been the legacy of the Global Financial Crisis? Using the concept of cultural memory, the project analyses how the most severe financial shocks of the last hundred years (1929-33, 1982, 1997, and 2007-9) have been remembered. The memory of financial crises will be retraced by exploring five interrelated areas, resulting in: the first comprehensive analysis of senior bankers' own views on financial crises; the first collective biography of the financial elite in the late 20th and early 21st century; a much clearer picture of the vision of

financial crises prevailing in the financial world and its evolution in the second half of the 20th century; a new light on the place of financial crises in the teaching of economics and finance; and new perspectives into the history and memory of financial regulation. By focusing on financial actors and combining economic history and cultural history, the project will provide a missing link in our understating of the recurrence of financial crises, thus pushing the boundaries of knowledge, renewing our understanding of financial crises and contributing to the ongoing search for greater financial stability.

SH-18. Social politics in European borderlands: A comparative and transnational study, 1870s-1990s

This project seeks to reframe the history of welfare and social care in modern Europe by restoring to view the contributions of local actors – primarily families and associations – to shaping welfare systems in three European borderlands: Galicia, the North-eastern Adriatic and the Franco/Belgian/German border regions. By focusing on the interactions among local actors and following developments from the late 19th century to the 1990s, this project turns our attention to the co-construction of welfare by public and private actors in highly mixed borderlands, where the reach of central states often fluctuated and a range of local welfare structures, based on national, but also non-national forms of identity/solidarity (e.g., occupation or religion) flourished. The focus on overlapping, and, at times, competing structures of social provision will allow me and my team to examine the interplays between inclusion and exclusion that have long shaped European welfare provision by zeroing in on those contexts where such competition was particularly visible. We will do this by placing intensively researched local studies in comparative and transnational frameworks, examining similarities and differences between north-western, eastern and south-eastern borderlands while tracing the circulation of ideas, people and practices. It is our conviction that the long-range historical study of local actors' ideas and practices around social welfare in European borderlands has much to tell us about the development of welfare across Europe in general. Our comparative and transnational analysis of the three borderlands will thus enable us to contribute constructively to contemporary societal debates about welfare reform at a time when the social rights (or lack thereof) of populations in Europe are the subject of acrimonious, even violent debate.

SH-19. The Wall: People and Ecology in Medieval Mongolia and China

Why did some (but not all) Chinese dynasties invest huge amount of resources in the construction of 'Great Walls'? The proposed project will focus on precisely that question, in an attempt to unravel what is perhaps the most enigmatic episode of 'Great Wall' construction. Roughly dated to the 10th-13th centuries CE and located far to the north of other 'Great Wall' lines, this Medieval Wall System (MWS) is one of the longest walls ever constructed in world history, stretching over more than 3,500 km and including large auxiliary structures (Fig. 1). The amount of resources invested in this MWS must have been enormous, but historical sources are mute about its construction, and modern scholarship is unable to date it precisely or understand why it was built and how it functioned. The motives behind the construction of the MWS, its political context and ecological implications, are highly relevant for the understanding of the complex history of China and Mongolia on the eve of Chinggis Khan's rise to power. However, because in the past scholars have assumed that 'Great Walls' were fortified border lines designed to stop military incursions, such issues' impetus and consequences were never addressed. Hence, the proposed project will put forward novel hypotheses, analyse them by using advanced recovery and analytical methods, and examine them against a broad archaeological, historical, environmental, and geographical background. The research hypothesis of the proposed project is that the MWS was not built as a defence against invading armies, but rather as a means to monitor and sometimes stop the movement of nomadic people and their herds. The large-scale movements of nomadic people towards more central areas of the empire happened, I would suggest, in times of ecological stress in the Steppe.

SH-20. Bloodborne: Hot Zones, Disease Ecologies, and the Changing Landscape of Environment and Health in West Africa

Why have certain regions, like West Africa, rich in biodiversity, also become identified as emerging disease hotspots in scientific and popular understanding? VIRHIST aims to discern the ecological, economic, political and social forces at play that have simultaneously turned certain regions into profitable sites of natural resource extraction, productive enclaves of biomedical research, and hot zones of pandemic threats. At its core, the project seeks interrogate how Western economic interests tied to natural resource extraction in West Africa produced new understandings about the ecology of disease, while simultaneously creating new environments and species relationships--in the laboratory and on the plantation--that eliminated certain diseases, but also creating conditions of possibility for other pathogens to thrive. VIRHIST offers a groundbreaking approach, stimulating cross-fertilization and interaction

across the fields of environmental history, medical history, and STS, to develop new perspectives on the history of environment and health. Through a focus on three bloodborne diseases—yellow fever, hepatitis B, and Ebola— at three distinct moments in West African history, VIRHIST advances the following research objectives: 1) Identify and substantiate the intended and unintended changes in disease ecologies produced through industrial plantations and biomedical interventions; 2) Interrogate the shifting ethics and economics driving emerging infectious disease research in West Africa in an age where biosecurity, surveillance, and pandemic anxieties mobilize significant resources and attention; and 3) Investigate the changing ethical, commercial, legal, and political standards that have shaped the collection and extraction of natural resources—from rubber, to chimpanzees, to viruses—in conservation and disease hotspots of the world.

SH-21. Algorithmic Societies: Ethical Life in the Machine Learning Age

ALGOSOC develops a new approach to understanding and responding to the consequences of machine learning algorithms for contemporary societies. Rapid advancements in machine learning technologies are transforming social and political life in ways that uniquely challenge how we live in relation to others. The life chances of a person are now intimately connected to the attributes that an algorithm has learned from the data patterns of unknown others. From judgements in the criminal justice system to decisions on treatment pathways in health, the outputs of algorithms have become pivotal to the decisions and adjudications on the probable futures of individuals. While there is substantial academic and public emphasis on defining ethical codes of conduct for algorithmic decisions, there is a lack of attention to how machine learning algorithms remake the ethical relations that define a society. In short, existing research is focused on limiting the harms of the actions of algorithms, whereas ALGOSOC focuses on how algorithms are redefining the thresholds of what harmful, good, bad, or risky behaviour means in a society. The ALGOSOC project will examine how 21st century machine learning algorithms are learning to recognize, to attribute, and to infer the characteristics of entities (people, groups, and objects). In order to do this, the project will conduct a series of path-defining studies of societal domains of machine learning that, though they share algorithms in common, have not previously been researched in combination: behavioural biometrics and biomedical object recognition; consumer recommendation and criminal justice scoring; oncology treatment pathways and anomaly detection for security. The ALGOSOC project will provide new social science knowledge of what is taking place as machine learning algorithms

travel across different domains and sites, and how precisely they learn by their exposure to different worlds of data.

SH-22. What drives human behavior regarding global coastal migration and adaptation in response to sea level rise and extreme flood events?

Future sea level rise (SLR), extreme flood events, and urbanization pressure will increase coastal flood risk, and in the absence of costly flood protection measures in numerous regions, millions of coastal residents will be forced to migrate to safer locations. This research addresses the significant challenge these trends pose to adaptation and migration policy: Which coastal areas will be protected, and in which regions will coastal migration become the inevitable adaptation option? To tackle this challenge, I propose focusing on the human adaptive and migration behavior of residents and other agents within one global framework by integrating (1) a global coastal flood risk model with (2) an agent-based model (ABM). Current global coastal risk assessment and migration methods do not address individuals' dynamic decisions regarding SLR and extreme flood events, and instead assume their adaptive behavior remains constant. However, the drivers that motivate people to migrate and adapt vary over time and space, and to capture these drivers (3) empirical data will be collected across seven surveys to parametrize realistic ranges for the behavioral rules in the ABM. (4) Novel global databases on flood protection, demography and socio-economy will be developed to extrapolate behavioral rules from the cases to other coastal areas. (5) State-of-the-art big-data methods using Twitter, mobile phone and IRS tax-filing data will be used to calibrate and validate migration patterns simulated by the global framework. The framework offers several advantages: high resolution (1x1km2) global migration, adaptation, and risk projections (2020–2100); novel maps of future migration hotspots; an improved understanding of what drivers (environmental, socio-economic, demographic, etc.) and interactions between stakeholders influence adaptation and migration decisions; and groundbreaking big-data validation. The framework will be used to assess adaptation and migration policies.

SH-23. Deep Decarbonisation: The Democratic Challenge of Navigating Governance Traps

The standard advice to politicians confronting long-term challenges such as decarbonisation is to adopt time-consistent commitment devices such as binding policies. Yet politicians appear unable to do this, greatly imperilling the achievement of the 1.5 and 2oC limits in the landmark Paris Agreement. The state-of-the art struggles to explain the causes, and hence the solutions,

to this impasse. Political scientists argue that politicians fear retribution at the next election; psychologists claim that citizens understand what is at stake, but expect politicians to lead. The untested assumption is that both are locked into a 'governance trap' which greatly reduces the political feasibility of rapid change. DeepDCarb seeks to significantly advance the academic state-of-the-art by directly interrogating the relationship between politicians, citizens/voters and other actors in a uniquely detailed and comparative manner, drawing on an unconventional combination of methods and unrivalled new data sets. It will establish a new subfield of interdisciplinary research that: • Explores the commitment devices that all states in the world have adopted, via a nested array of 13 new datasets and time-sensitive statistical techniques; • Opens up the 'black box' of societal commitment formation in a sample of large emitters (including the EU-28) to explore the relationship between politicians and citizens (1990-2020); • Investigates the scope for unlocking traps by bringing actors together in deliberative fora such as citizens' assemblies, thus confronting the uncomfortable question of how far societal commitment is more effectively engendered by depoliticising or politicising contentious issues. The findings, to be widely disseminated through a programme of publication and public engagement, will contribute significantly to understanding the scope for unlocking the profound impasse in society's struggle to deliver deep decarbonisation.

SH-24. Building Arctic Futures: Transport Infrastructures and Sustainable Northern Communities

The "new Arctic" is attracting global attention for a variety of reasons, including geopolitics, militarisation, resource extraction, wilderness tourism, and calls for environmental protection in the face of rapid climate change. Many of these activities necessitate the construction or upgrading of transport infrastructures in this relatively remote, inaccessible and scarcely-populated part of the world. While these large-scale infrastructures are mostly sponsored by outside interests, they can have profound impacts on local residents. We propose to focus on how residents of the Arctic, both indigenous and non-indigenous, engage with these infrastructures, and to examine the intended and unintended consequences these projects have on their lives. Our challenge is to understand whether existing and planned transport infrastructures will support permanent human habitation and sustainable communities in the Arctic, or whether they will strengthen a trend of substituting permanent residents with "temporaries" like shift workers, tourists and military personnel. In addressing this challenge, we adopt a relational affordance perspective, which will document the material and non-material entanglements of local residents and transport infrastructures in three distinct arctic

regions. Our approach combines ethnographic fieldwork with mapping exercises and archival research. Our project team of anthropologists and geographers will use quantitative population data to upscale to the regional level, and regional patterns will be contrasted and compared to reach conclusions on the panarctic level. We will use interactive scenarios to collect input and to develop decision options. Our overarching research question – What is the role of transport infrastructures in sustaining arctic communities? – is of urgent relevance on both theoretical and practical levels, and by addressing it we will contribute locally informed results to critical conversations about arctic futures.

SH-25. Intergovernmental Organizations between Mission and Market: International Institutional Law and the Private Sector

Intergovernmental organizations (IGOs) such as the World Health Organization or International Maritime Organization have always been assumed to work for the public good. Yet, they also engage the private sector in many ways. Some are funded by the private sector or set up public-private partnerships; IGOs themselves act and compete on markets when procuring goods and services or when marketing their own services; and their operations and standard-setting activities inevitably affect the distribution of benefits between private parties. Like most organizations, IGOs allocate costs and benefits, and therewith affect the private sector. IGOs are said to exercise functions on behalf of member states and for the public good, yet the encounter with the private sector may see them act in tension with this public mission. PRIVIGO will investigate this tension, first, by examining how widespread private sector involvement is and how IGO law responds to this involvement. Second, PRIVIGO will examine how the underlying framework of the law is affected: the legal rules are informed by theoretical considerations that are, in turn, informed by assumptions and axioms that are rarely questioned yet may be fundamentally irreconcilable with private sector involvement. In this manner, PRIVIGO will change how IGO law and IGO lawyers perceive and understand IGOs, renewing IGO legal theory. PRIVIGO will build on case studies conducted in eight different and varied domains where IGOs with a clear public mission are active and connections to the private sector are visible: food security; transportation; energy provision; health; human re-settlement; finance; resources and environment; and arms control. PRIVIGO aims to develop the law relating to IGOs and build up solid theoretical foundations, mindful of the huge impact of IGOs on our everyday lives.

SH-26. Problem Definition in the Digital Democracy

"How does an issue become a political problem? No issue inherently requires political responses. Instead, political actors construct arguments regarding the nature of a given problem and connect them to particular policy actions. For example, and to preview PRODIGI's substantive focus, some see digital technology as a threat to democracy and advocate for stricter regulation, while others emphasize its potential to improve participation and argue that tighter rules stifle innovation. This phenomenon, known as ""problem definition,"" has long been recognized as a fundamental aspect of any policymaking process. Theoretically, PRODIGI argues that the notion of problem definition needs to integrate the dynamics induced by digital technology, such as new forms of political communication that bypass traditional gatekeepers. The state of the art does not adequately describe these new dynamics. On the one hand, the literature on digital technology and politics has not explicitly recognized problem definition as a a key aspect. On the other hand, the agenda setting and problem definition literatures have not integrated the role of digital technology in their arguments. Specifically, PRODIGI pursues four objectives: 1) develop a theory of problem definition that accounts for the role of digital technology; 2) develop new methods to measure problem definition based on computational social science; 3) analyze problem definition in the case of policy responses to digital technology's implications for democracy; and 4) analyze the effects of problem definition on opinions using survey experiments. PRODIGI breaks new ground in two ways. First, it puts forward original theory and methods to study a longstanding question that has acquired new relevance in digital environments. Second, it applies the new theory and methods to an important societal challenge, namely, how politics responds to digital technology's impact on democracy."

SH-27. Re-orienting development: the dynamics and effects of Chinese infrastructure investment in Europe

REDEFINE will examine what China’s rise means for how we understand global development and, specifically, Europe’s place in it. After 15 years of ‘going out’ to access raw materials and new markets, often in the global South, China is making assertive moves into developed economies, which were boosted by the Belt and Road Initiative linking China to Europe. At the same time, many European economies stagnated following the 2008 financial crisis with governments cutting infrastructure investment and seeking alternative sources of finance. China now sees Europe as fertile ground for new infrastructure investment, yet many European firms

and governments are ill-equipped to deal with these political and economic changes. The first wave of Chinese internationalisation into the global South has been analysed largely from the perspective of international Development Studies. In the current phase, China's move westwards radically questions the meanings and loci of development. REDEFINE's innovation is to use insights from international development to interrogate Chinese engagement in the heart of Europe and by doing so re-orient the Eurocentric debates in the social sciences around how we define and delimit development, who drives these processes, and what it means for societies affected by such investments. REDEFINE's aims require a disaggregated approach to unpack project-by-project effects, which will be undertaken using an assemblage methodology. Through comparative, ethnographic case studies in the UK, Germany, Greece and Hungary REDEFINE will produce fine-grained analysis to understand the rationales for Chinese investment in Europe, the geopolitical dynamics surrounding these financing streams, the structuring of projects, and how they interface with national and local development policy. By better understanding how investment deals operate, REDEFINE will connect Chinese and European government and corporate actors in order to influence their strategies and practices.

SH-28. The Transnational Divide: Local Triggers, Social Networks, and Group Identities

TRANSNATIONAL seeks to explain a surprising and consequential feature of contemporary democratic politics—the intensity of polarization on immigration, Europe, and climate change. While recent research has made impressive advances in understanding individual attitudes and party-political competition, there is currently no empirically verified theory of how a person's social context shapes their response to issues that arise on the political agenda. Without such a framework we cannot understand the rising incidence of group solidarity and affective polarization in our societies. TRANSNATIONAL combines insights from the literatures concerned with networks and identity formation to theorize the social contexts in which people respond to major events. This approach provides a micro-social foundation for Lipset & Rokkan's classic cleavage analysis and offers the prospect of a unified theory of political conflict. TRANSNATIONAL gains inferential leverage in the face of causal complexity by linking national surveys, natural experiments, and semi-structured interviews in three modules. The first module provides a comparative frame by conducting a cross-sectional survey of political attitudes, identities, and digital and face-to-face networks on the transnational divide in six countries. Modules 2 and 3 drill down by devising natural experiments that allow deep investigation of how local populations respond to a specific situational trigger. These are a)

spatial proximity to refugee housing; b) the variable effect on UK localities of exit from the EU; c) new climate impact scores that differentially affect rural and urban localities.

SH-29. Monitoring Biodiversity from Space

Life, with all its diversity, is in crisis. As humans increasingly encroach on biologically complex semi- natural landscapes, no organism, place or ecological function remains unaffected. While all 196 parties (195 countries plus the European Union) to the UN Convention on Biodiversity (CBD) have agreed to monitor the state of biodiversity, the currently available methods to do so leave much to be desired. Traditional monitoring involves the field observation of species by trained specialists, aided by skilled volunteers, whose expertise is restricted to specific biotic groupings. In a process that is both time consuming and inconsistent across time and space, botanists identify and record the presence of plant species and ornithologists the bird biota, resulting in 'unpopular' biotic groups such as fungi, bacteria and insects being under-observed or escaping identification altogether. In this project, a fundamentally different approach to terrestrial biodiversity monitoring couples next generation satellite remote sensing with environmental DNA (eDNA) profiling, complemented where available by legacy human-observed datasets. Satellite remote sensing is able to survey the environment as a single, continuous, fine-resolution map, while eDNA profiling can rapidly quantify much greater taxonomical and functional breadth and depth than human field observation. This project combines, for the first time, these two powerful, cutting-edge techniques for monitoring biodiversity at the global level in a consistent manner. Following from this, another key innovation will be the deepening of our scientific understanding of how biodiversity is impacted by anthropogenic pressure as well as by natural environmental gradients. In concert, these scientific developments will enable the accurate and fine grain monitoring of biodiversity from space – a ground-breaking contribution to the quest to meet the UN Sustainable Development Goals and CBD Aichi targets.

SH-30. Rethinking China's Model of Urban Governance

China's phenomenal urbanisation is of world-historical significance and imposes profound theoretical and policy challenges. This ground-breaking project will rethink China's model of urban governance through grounded and multi-scalar investigations ranging from neighbourhoods and cities to regions. For neighbourhoods, it unravels the interface between state and society in everyday living space, migrant social agencies and the self-governance of

homeowners' associations under urbanisation and housing marketization. For cities, it interrogates the development strategies and governance of migrant and ecological urbanism as well as the implementation of projects through financial instruments and the land market. For regions, it uncovers entangled state–market relations which redistribute population and economic activities across cities and produce the city-region. The research will be conducted through six cases: Shanghai, Wuhan, Dali, Xiongan, Jing-Jin-Ji (Beijing-Tianjin-Hebei), and the Guangdong–Hong Kong–Macau Greater Bay Area, based upon grounded ethnographic observations, in-depth interviews and close engagement with Chinese researchers and policy makers across different types of neighbourhoods and cities of varying sizes in coastal, central and western regions, and recent national strategic projects. The project is timely for China to implement a UN-endorsed new urban agenda and rethink its model in the face of trade tensions. It will change how we think of China and its governance and be the first of its kind to explicitly consider indigenous perspectives on Chinese urban transformation. This innovative and contextually sensitive research will contribute to entrepreneurial urban governance theories and will offer a theoretically nuanced and grounded explanation of state entrepreneurialism in China, with six workshops organised within China as integral parts of knowledge production as well as a series of publication outputs.

Life sciences (LS) sub-corpus

LS-1. Next Generation Gene Therapy for the Treatment of Chronic Myocardial Ischemia and Heart Failure

BACKGROUND: Therapeutic angiogenesis has great potential for the treatment of severe heart diseases. However, this requires novel approaches and development of new technology. ADVANCING STATE-OF-THE-ART: We will develop novel VEGF-B and VEGF-C-based gene therapy to treat refractory angina and heart failure (HF). VEGF-B and VEGF-C lead factors were selected from extensive pig studies where they showed the best benefits among all VEGFs, such as relative cardiac specificity, potent angiogenic and metabolic effects (VEGF-B) and lymphangiogenic activity (VEGF-C). Exogenous gene transfer and new endogenous gene activation technology will be developed. Key new technologies are riboswitch-regulated-AAV8 vectors, Super-Enhancer driven cell-type targeted gene expression, VEGF-B and VEGF-C designer mutants for better efficacy and activation of natural endogenous VEGF-B and VEGF-C expression with promoter binding shRNAs, circRNAs, CRISPR/mutantCas9-VP64-SAM gene activation technology and using a novel concept of the release of promoter pausing. Immunological concerns of AAV8 and usefulness of new synthetic dendrimer carriers will be addressed. HeartGenes utilizes optimized percutaneous intramyocardial and retrograde

venous gene delivery in pig chronic ischemia and HF models, clinically relevant pig exercise test, and 15O-H2O and 18F-FDG PET/MRI imaging to detect treatment effects. Simultaneously, HeartGenes will take a realistic approach to clinical translation and starts intramyocardial vs retrograde venous riboswitch-AAV8-VEGF-B186 phase I trial in refractory angina as the first step to bring the best novel constructs and the most advanced functional and imaging endpoints developed in HeartGenes to clinical testing at the end of the project. SIGNIFICANCE: If successful, this approach will bring a paradigm shift to cardiac gene therapy and new therapeutic options for heart diseases. Novel new technologies may also become widely applicable in other areas of medicine.

LS-2. Inhibiting BAF to Improve Gene Delivery

Safe and efficient delivery of nucleic acids to tissues and cells is a shared challenge in the clinical translation of gene therapy and gene editing. At the intracellular level, DNA delivery is hindered by endo/lysosomal sequestration, inefficient transport into the nucleus and a retention mechanism mediated by the barrier-to-autointegration factor (BAF) protein that detects, clusters and locks away intruding double-stranded DNA in membrane cages. The first two of these intracellular obstacles are well-known bottlenecks and are being addressed by many laboratories. However, preliminary in vitro data suggest the detrimental impact of BAF's mechanism on transgene expression is underestimated. We hypothesize that transiently suppressing BAF or one of its regulating factors will increase the cytosolic availability and mobility of transfected DNA, facilitating its transport to the nucleus and ultimately boosting transfection efficiency. We will tackle this rather uninvestigated mechanism through two parallel strategies: i) identifying novel small-molecule inhibitors of BAF or its regulators via high-throughput screening of chemical libraries, and ii) producing a recombinant kinase that phosphorylates BAF in situ and thus supresses its DNA-clustering function. The BAF suppressors will be co-delivered to cells with rationally-designed nucleoprotein nanoparticles consisting of a reporter plasmid and a dual-function fusion protein to facilitate endocytosis and endosomal escape. The combined transfection-enhancing effect of the BAF suppressors and the nanoparticles will be extensively characterized in vitro, and in vivo proof-of-concept will be obtained in mice. Besides expanding our fundamental knowledge on this unexplored DNA retention mechanism, the project will provide powerful transfection enhancers that can boost already-existing gene delivery platforms (viral and non-viral), so that these can reach their full potential for gene therapy and gene-editing applications.

LS-3. High-Dimensional single cell mapping of inflammatory disease signatures in monozygotic twins

Multiple Sclerosis (MS) is a chronic inflammatory disease, where immune cell invasion into the central nervous system causes immunopathology and neurological deficit. Although disease-modifying therapies dramatically reduce disease activity, they hold the potential for severe adverse effects while long-term disability prospects remain poor. Moreover, there is to date no biomarker for monitoring the disease activity and to guide therapy decisions. I propose that the key to identifying such biomarkers is to combine single-cell mapping of leukocytes across well-curated patient cohorts with unbiased machine-learning based data interrogation. Using such an approach, we have already delineated a disease signature in a helper T cell population specific for MS. However, the immune compartment of cross-sectional cohorts is influenced by the individual genetic make up, which masks disease-specific signals and hinders a more precise characterisation of involved immune cell populations. To eliminate genetic influences, I here propose in aim 1 to interrogate the immune compartment of a unique cohort of monozygotic twin pairs -discordant for MS- and deeply analyse peripheral blood lymphocytes by single-cell mass cytometry, combined TcR and single cell sequencing, and epigenetic profiling. aim 2 to develop representation-learning methods to account for the paired genetics of twins or longitudinal samples and to include clinical covariates into the high-dimensional data set. aim 3 to use well-defined patient samples of MS-like disorders (MS-Mimics) and longitudinal samples of patients undergoing disease-modifying therapy (e.g. B cell depletion, autologous stem cell transplant) using single-cell mass cytometry. Ultimately, the goal is to reduce the dimensionality of disease signature(s) towards a clinically translatable low-dimensional biomarker that could be identified and quantified by routine methods available in the clinics.

LS-4. Targeting cancer vulnerabilities in acute leukemia

Background and rationale: Adult acute leukemias pose a great challenge to cancer therapy, with only few advances made in 50 years. As these malignancies are commonly associated with multiple epigenetic aberrations, epigenetic factors represent attractive leukemia drug targets. Nevertheless, most epigenetic-targeting drugs have displayed limited clinical benefit and key leukemia drivers like MYC, ERG and MYB remained mostly undruggable. We have developed a new class of small molecule kinase inhibitors, termed “oncodestroyers” (ODs), single

molecules combining supreme p53 activation with selective disruption of multiple leukemia-specific super-enhancers (SEs) that drive oncogenes and dependency/vulnerability factors. These inhibitors demonstrate an unprecedented therapeutic potency in mouse models of human leukemia and are entering now leukemia clinical trials. With this project we wish to study the principles of "oncodestruction", mechanisms of drug action, immune system interface, and preempt drug resistance. Relevant knowledge may be applied to other cancer diseases, sharing vulnerabilities with leukemia. Major Goal: To expand the therapeutic potential of ODs in leukemia and pre-leukemia by studying their vulnerability basis, mechanisms of drug action and indicators of therapeutic response in individual patients. Research plan: 1) Expand the collection of small molecule kinase inhibitor ODs and develop OD-based PROTACs to gain an optimal spectrum of kinase targets with good therapeutic window in AML; 2) Elucidate the mechanisms of action and what distinguishes an OD, with emphasis on SE disruption, p53 activation and OD-immune-cooperation; 3) Explore the translational aspects of OD treatment by: identifying OD resistance and relapse mechanisms; study clonal evolution in MDS and AML patients undergoing phase 1a/b clinical trial; predict a patient response to ODs and use ODs for ameliorating age-related clonal hematopoiesis, thus possibly averting leukemogenesis.

LS-5. A PRECISION CELL REPLACEMENT STRATEGY FOR PARKINSON'S DISEASE

Parkinson's disease (PD) is a progressive incurable neurodegenerative disorder characterized by the loss of substantia nigra neurons (A9/SNs), a subset of midbrain dopaminergic neurons (mDAs) that are required for functional re-innervation of the striatum. Current treatments for PD are symptomatic and do not prevent disease progression. Proof-of-concept clinical studies using human fetal midbrain tissue for transplantation have shown that replacement of mDAs can change the course of PD. Human pluripotent stem cells (hPSCs) are currently used to generate mDAs for cell replacement therapy in clinical trials. However, our single-cell RNA-sequencing analysis of these preparations revealed that they comprise a complex mixture of cell types, including mDAs but also excessive vascular progenitor-like cells and serotonin neurons, thought to drive dyskinesias. Selective generation of A9/SNs for PD cell replacement therapy remains thus a major challenge. Here I propose to identify how human adult A9/SNs are generated in order to develop a novel cell type-specific precision cell replacement therapy for PD. I hypothesize that a yet undefined network of transcription factors and regulators control A9/SN subtype specification, and that such factors can be used to engineer A9/SNs starting from hPSCs or astrocytes, moving the field beyond the state of the art. This will be achieved by: 1) Using cutting-edge CRISPR and single cell methodologies to identify the factors

controlling the specification of human A9/SNs; and 2) developing two novel cell replacement strategies for PD, involving either transplantation of hPSC-derived progenitors forward-programmed into A9/SNs or reprogramming of endogenous striatal glia in situ into A9/SNs, using a method we recently developed. I expect PreciseCellPD will generate groundbreaking knowledge of the mechanisms controlling the generation of human A9/SNs and will set the basis of a novel and transformative precision cell replacement therapy for PD

LS-6. MOVING FROM BIOMARKERS TO MECHANISM ORIENTED PREVENTION OF CARDIOMETABOLIC DISEASE

Increasing occurrence of obesity and diabetes is the major threat to cardiovascular health of our century. Whereas the field is saturated with "omics" strategies aimed at improving prediction of cardiometabolic disease (CMD), mechanism-orientated prevention strategies, which is what the population calls for, are lacking. We here propose three completely new and high-risk strategies to prevent CMD in large subsets of the population, who have elevated risk due to measurable endocrine abnormalities. SUBPROJECT 1: We test if the increased CMD risk linked to high levels of the intestinal fat absorption and storage promoting hormone neurotensin (NTS), can be improved by: (A) blockade of NTS using monoclonal antibodies in mice and (B) inhibition of NTS secretion and intestinal fat uptake with the drug orlistat in humans. SUBPROJECT 2: High plasma levels of vasopressin (VP) (present in 25% of the population) is a strong risk factor for later CMD and the dominating cause of high VP is low water intake. We therefore test if the elevated CMD risk in subjects with high VP can be reduced by increasing water intake in a large 12-month randomized trial of 1.5 L water supplementation vs control therapy. SUBPROJECT 3: Aderenomedullin (ADM), whose endothelial secretion is enhanced in obesity, has beneficial effects on the intravascular wall but in the extravascular space, to which it diffuses freely, it may promote diabetes. We investigate how long-term increase and decrease of levels of bioactive ADM in the intra- and extravascular compartments, respectively, affect atherosclerosis and glucose metabolism in mice. In humans we test if a monoclonal antibody, which traps ADM in the circulation (while still allowing it to bind to its endothelial receptors) and drains it from the extravascular space, improves vascular function and glucose metabolism. We provide completely novel, mechanism-orientated and near-future applicable strategies for primary prevention of CMD.

LS-7. Targeting auto-reactive B-cells by vaccination to cure human auto-immune disease

Currently, most human autoimmune diseases are chronic conditions without a prospect of cure. My aim in this proposal is to meet the next major challenge, achieving cure in autoimmune disease. Many autoimmune diseases are characterized by autoantibodies and are remarkably responsive to B-cell targeted therapies, demonstrating that the autoreactive B-cell is central to disease pathogenesis. Nonetheless, the selective and permanent elimination of the autoreactive B-cell, both memory and plasma cells alike, is not presently feasible due to a lack of specific markers and treatments. My aim is to develop a vaccine that will allow the specific and long-lasting depletion of autoreactive B-cells, thereby inducing cure. Using the unique mutated sequences of autoreactive B-cell receptors (BCR), cytotoxic T-cells that specifically eradicate autoreactive B-cells will be induced. This concept extends the remit of vaccines beyond infectious diseases and cancer, into the sphere of autoimmune disease. Using the well-defined autoimmune disease rheumatoid arthritis (RA) as prototype, I will study the RA-specific autoimmune response. Our recent findings show that RA is characterized by a restricted, oligoclonally-expanded autoreactive B-cell pool. Using recently developed technologies, my team will identify autoreactive B-cells and the BCR repertoire at several (pre)disease stages. We will then determine the potency of the many non-germline-encoded mutations in BCRs as “neoantigens” amenable to T-cell recognition and vaccination. Incorporating these neoantigens into multiple long peptides covering the autoreactive B-cell repertoire, we will design patient-tailored vaccines and perform a phase I trial to determine the feasibility of specifically depleting disease-causing B-cells. This research will create the possibility for patient-tailored vaccines that can permanently eradicate auto-reactive B-cells in B-cell driven auto-immune diseases; diseases that are still incurable to date.

LS-8. Targeting the essentialome of radiotherapy-resistant cancer

"More than 50% of the cancer patients undergo irradiation as part of their cancer treatment. Although radiotherapy (RT) significantly contributes to cancer cure, local therapy resistance and the subsequent emergence of distant metastasis remain major obstacles for its success. The molecular mechanisms underlying tumor cell-intrinsic RT resistance are ill-defined. It is therefore crucial to better define these mechanisms and identify new vulnerabilities of RT-resistant tumors in order to decrease the current annual cancer mortality of >1.3 million persons in EU member states alone. In the TETHER project, I will address the problem of RT resistance by synergizing the power of genetic essentiality analyses with unique mouse models and organoids that we have established. We recently found that members of the shieldin and CST complexes are essential for tumor cells to survive irradiation, while causing PARP inhibitor

resistance when lost in BRCA1-deficient tumors. Based on this unexpected finding, I have started a new line of research to dissect the RT ""essentialome"". As I show with the discovery and functional characterization of ERCC6l2 as a novel DNA repair factor in this network, the technology we have in place is perfectly suited to tackle this question. In addition, we will apply distinct CRISPR/Cas9-based tests to map the functional interactome of genes that are essential for RT resistance. To follow the plasticity and RT escape of tumor cells in vivo, we have also developed innovative model systems. Similar to the situation in cancer patients, we observe that residual cancer cells in our mouse models escape the deadly effects of RT by local resistance or metastasis formation. Thus, these models provide a unique opportunity to explore and target RT escape mechanisms. I am convinced that the combination of these state-of-the-art approaches will yield highly useful information for designing individualized approaches to improve RT response in cancer patients. "

LS-9. Immune-privileged, immortal, myogenic stem cells for gene therapy of Muscular Dystrophy.

Duchenne muscular dystrophy (DMD) is a devastating incurable disease, affecting thousands with heavy burden on health systems. This project combines the development of a safe, “immune-privileged cell” with genetic engineering to correct many dystrophin gene mutations for an efficacious and cost affordable therapy. The applicant pioneered systemic intra-arterial transplantation of mesoangioblasts (blood vessel-derived progenitors) that proved safe in DMD patients and is being implemented for efficacy. However, this personalised approach would prove prohibitively expensive for healthcare systems, as pricing of successful gene therapies is showing. We made the striking observation that human mesoangioblasts can be indefinitely expanded with a novel culture medium, even after genetic manipulation and cloning. Cells will be first genome edited to delete endogenous HLA (β2-microglubin and class II CTA) while inserting tolerogenic HLA-E, fused to β2-microglubin and, as safety device, the Herpes Simplex Thymidine Kinase suicide gene with truncated NGF receptor for selection. Edited clones will be checked for genome integrity. Selected clones will be engineered to express a small nuclear RNA (snRNA) that causes skipping of a given exon of the dystrophin gene. Due to the syncytial nature of muscle fibres, the snRNA also enters and corrects the genetic defect in neighbouring, dystrophic nuclei, thus amplifying of one log the therapeutic effect. Five different cell lines would correct the mutation in 60% of DMD patients. The cell lines will be transplanted in humanized DMD mice and assessed for the ability to escape immune surveillance and to differentiate in dystrophin expressing myofibers, establishing pre-clinical

safety and efficacy for an off the shelf, affordable product. The applicant has unique expertise to successfully complete this project, whose strategy may be expanded to other recessive monogenic diseases, for a ground breaking impact in regenerative medicine.

LS-10. Brain metastases: Deciphering tumor-stroma interactions in three dimensions for the rational design of nanomedicines

Brain metastases represent a major therapeutic challenge. Despite significant breakthroughs in targeted therapies, survival rates of patients with brain metastases remain poor. Nowadays, discovery, development and evaluation of new therapies are performed on human cancer cells grown in 2D on rigid plastic plates followed by in vivo testing in immunodeficient mice. These experimental settings are lacking and constitute a fundamental hurdle for the translation of preclinical discoveries into clinical practice. We propose to establish 3D-printed models of brain metastases (Aim 1), which include brain extracellular matrix, stroma and serum containing immune cells flowing in functional tumor vessels. Our unique models better capture the clinical physio-mechanical tissue properties, signaling pathways, hemodynamics and drug responsiveness. Using our 3D-printed models, we aim to develop two new fronts for identifying novel clinically-relevant molecular drivers (Aim 2) followed by the development of precision nanomedicines (Aim 3). We will exploit our vast experience in anticancer nanomedicines to design three therapeutic approaches that target various cellular compartments involved in brain metastases: 1) Prevention of brain metastatic colonization using targeted nano-vaccines, which elicit antitumor immune response; 2) Intervention of tumor-brain stroma cells crosstalk when brain micrometastases establish; 3) Regression of macrometastatic disease by selectively targeting tumor cells. These approaches will materialize using our libraries of polymeric nanocarriers that selectively accumulate in tumors. This project will result in a paradigm shift by generating new preclinical cancer models that will bridge the translational gap in cancer therapeutics. The insights and tumor-stroma-targeted nanomedicines developed here will pave the way for prediction of patient outcome, revolutionizing our perception of tumor modelling and consequently the way we prevent and treat cancer.

LS-11. Redesigning brain circuits in development

In the pre-optogenetics era, molecular genetics defined the concepts of neural circuit development providing mechanistic insights into axon guidance and synapse assembly. However, this approach often revealed limited insights into the function of the circuits studied.

Since 2005, optogenetics has revolutionized our approach to functionally dissect brain circuits and has tremendously increased our understanding of how they contribute to specific behaviours. However, how these circuits assemble during development remains mostly unknown. Here, I propose to combine these two approaches: to genetically redesign specific circuits during mouse development in a predictable fashion, and to test the consequences for innate and learned behaviour. This novel line of research follows concepts of synthetic biology, which aims at reconstructing cellular systems, with the intention of redesigning brain circuits to reroute information processing for new behavioural purposes. We aim to demonstrate that targeted mis-expression of connectivity signals can alter specific neural circuits and communications between circuit components along measurable hypotheses. Activation of such an artificial circuit, by either natural stimuli or optogenetics, is likely to produce a set of behavioural outcomes that will reveal general connectivity rules, the capacity for behavioural plasticity, and possible functional redundancies between circuits. Anatomical and physiological dissection of the redesigned circuit will reveal to what extent the incoming afferents instruct the target cells to produce their output responses. Our focus will be on the amygdala, a forebrain structure necessary for processing aversive and rewarding stimuli and orchestrating behavioural responses, and a brain circuit characterized by a high degree of cellular heterogeneity and interconnectivity. Overall, this work will provide important insights into the principles of developmental circuit wiring in the mammalian brain.

LS-12. Assembly and plasticity of inhibitory cortical networks by early learning experience

The extraordinary diversity of animal behaviors relies on the precise assembly and fine-tuning of synapses in neuronal circuits that adapt to an ever-changing environment. Hence, mature networks are the final expression of experiences accumulated throughout our life. Importantly, young brains are more amenable to learning that older brains, but the neural mechanisms underlying these differences remain largely unknown. In the cerebral cortex, for example, there are two main classes of neurons, excitatory projection neurons (pyramidal cells) and inhibitory neurons (interneurons). Interneurons have a remarkable capability to sense changes in sensory experience and therefore occupy a unique position to orchestrate circuit remodeling. The goal of this project is to understand the mechanisms through which enhanced sensory experience during development sculpts cortical circuitries to improve behavioral performance in mice. To this end, we will use: (1) a synaptic connectivity mapping strategy (e-GRASP) and an activity-dependent promoter to explore specific cell- and synaptic-specific reorganizations driven by sensory experience; (2) sensory discrimination tasks and two-photon microscopy to explore the

emergence of cortical functional properties, cell ensembles and behavioral performance; (3) unbiased screenings in cell populations and specific synapses together with single-cell RNA sequencing to identify genes that regulate cell-type specific modifications; and (4) loss of function approaches (shRNA and CRISPR/Cas9) to analyze the role of the identified candidate genes. Our research will shed light on the mechanisms shaping the assembly and function of cortical circuitries during early sensory experience.

LS-13. Convergence of positive and negative reinforcement in fentanyl addiction

F-Addict strives to unravel the neural circuits driving compulsion in fentanyl addiction. We ask the question how fentanyl causes fast transition from medical or recreational controlled drug use to compulsive consumption. About a third of opioid users eventually loose control, which increases the risk of death by overdose; a number that is even higher for fentanyl and definitely exceeds the transition observed with psychostimulants. The neural correlate of this difference remains elusive. We posit that repetitive withdrawal leads to strong negative reinforcement, which in conjunction with inherent positive reinforcement favors the transition to compulsion. F-Addict will uncover the synaptic processes and neuronal population activity leading to addiction in a mouse model of oral fentanyl self-administration. Much preliminary data implicate activity in the mesolimbic dopamine system and upstream subcortical regions (paraventricular thalamus/habenula/basolateral amygdala) in positive and negative reinforcement, respectively. In addition, top down control, in particular by the orbitofrontal cortex may drive compulsive drug use. The proposed project will harness advanced circuit investigations for an innovative, original perspective: how does positive and negative reinforcement in fentanyl addiction contrast with current circuit models of addiction that are based on psychostimulants? In a translational spirit, F-Addict will also examine the effects of oral substitution with methadone and buprenorphine, recognized therapies for opioid addiction. Much preliminary data provides proof of feasibility and principle. We are confident that our approach at the frontiers of modern neurosciences carries the potential for groundbreaking results to answer a timely question. Unraveling the neural basis of fentanyl addiction will enhance the molecular understanding of circuit modulation to shape future therapies facing the still growing opioid epidemic.

LS-14. Holographic control of visual circuits

The aim of this research program is to produce novel all-optical technologies to explore brain functions at the mesoscopic scale with cellular resolution opening a new phase in optogenetics that I named circuit optogenetics. Revealing the neural codes supporting specific mammalian brain functions is a daunting task demanding to relate in vivo the individual activities of large numbers of neurons recorded jointly within collectives that form distinct nodes of a network and to perform precisely targeted and calibrated interventions in the spatiotemporal dynamics of neural circuits on the scale of naturalistic patterns of activity. Despite recent technical advances, these experiments remain out of reach because we lack a comprehensive approach for large-scale, multi-region, in depth, single cell and millisecond precise manipulation of neural circuits. HOLOVIS will tackle these limitations through the construction of an innovative paradigm combining optogenetics with cutting-edge technology of wave front shaping, compressed sensing, microendoscopy, wave-guide probes, laser developments and opsin engineering. My lab has pioneered the use of wave front shaping for neuroscience and developed in the past years a number of new optical methods, for patterned optogenetic neuronal stimulation. Here, we will push forward this technology and first demonstrate the performances of these breakthrough systems to reveal how inter, intra-laminar and cortical/sub-cortical wiring construct and refine visual orientation selectivity in mice. We will focus on the visual system of mice, whose input-output responses to controlled sensory stimulations have been characterized in decades of studies. However, we are persuaded that our approach can be used to reveal the connectivity rules that underlie specific patterns of activity of any neuronal circuit, thus defining the functional building blocks of distinct brain areas.

LS-15. The human retina at single cell resolution: functional architecture, disease mechanism and therapy development

Vision is of key importance for humans and losing vision has a major effect on day-to-day life. Vision starts in the retina, where an image captured by photoreceptors is processed by retinal circuits built from more than hundred cell types. Information flows from the retina via the thalamus to a number of cortical areas. Despite the large number of cortical neurons involved in vision, most blinding diseases originate in the retina and are cell-type specific. Although the vertebrate retina has a conserved cellular architecture, only a few animal models of visual diseases reproduce the pathology found in humans. Therefore, there is a major need for understanding the healthy and the disease-affected human retina. Recently my laboratory developed a set of new technologies that enable us to study the human retina, to understand its functional architecture and disease mechanism in its cell types, and so to develop therapies.

Using these technologies, we first aim to describe the functional diversity as well as the function of ganglion cell types and their circuits in the human retina. Second, we aim to reveal mechanisms of cell-type vulnerability in human and mouse retinas. Third, we aim to provide proof of principle for cell type-targeted near infrared vision restoration in the human retina. Taken together, this study will provide insights into the structure, function, and mechanisms of disease of the cell types in the human visual system and will investigate a new approach to restore vision in patients with blinding diseases.

LS-16. Intrinsic and extrinsic determinants of neuronal identity

Neuronal diversity determines the variety of circuits that can be formed and thus sets the framework for an animal's behavioural repertoire. During development, distinct neuronal types emerge from interactions between cell-intrinsic processes and cell-extrinsic processes. In the brain, untangling how intrinsic and extrinsic processes contribute to neuronal identity has been difficult, as neurons are highly interconnected and heterogeneous cells with distinct and dynamic sensitivities to environmental signals. In such conditions, high temporal single-cell resolution approaches are required to parse out the drivers of cell-type differentiation. The mouse neocortex is an ideal model to tease out drivers of differentiation: radially, cell-intrinsic genetic mechanisms drive the generation of successive neuron types across cortical layers; tangentially, cell-extrinsic processes are critical to drive differentiation via synaptic input across cortical areas. Here, using the developing neocortex as a model system, I propose to identify how cell-intrinsic and -extrinsic processes interact to define distinct neuron identities by characterizing: 1. emergence of area-specific neuronal and progenitor identities using FlashTag fate mapping and single-cell RNA sequencing (Work Package (WP) 1) 2. plasticity of area-specific neuronal states in response to genetic manipulation, transplantation or input/activity manipulation (WP2) 3. spatial context-independent components of neuron identity, by uncovering core molecular and circuit states in vitro (WP3) 4. postnatal experience-dependent controls over neuronal identity, using the precocial rodent Acomys as a new model to study the role of early brain-world interactions (WP4). Together, these experiments aim to identify the molecular determinants of progenitor and neuron types by distinguishing intrinsic and extrinsic drivers of cell identity, with the long-term aim of reverse-engineering tailored neuronal cell-types for circuit repair.

LS-17. Mechanisms of Presynaptic Biogenesis and Dynamic Remodeling

Our ability to move, to process sensory information or to form, store and retrieve memories crucially depends on the function of neuronal synapses. Synapses comprise a presynaptic compartment harboring the machinery for neurotransmitter release and an associated postsynaptic compartment that processes the neurotransmitter signal. During decades of research we have acquired a wealth of knowledge regarding the mechanisms of neurotransmitter release and information processing in the postsynaptic compartment. In great contrast, we know surprisingly little about the pathways that direct the formation, transport, and assembly of the complex molecular machines that make up a functional presynapse. In particular, it is unclear where and how synaptic vesicle (SV) precursors are formed in the neuronal cell body, in which form they are transported along the axon, and which maturation steps occur to allow their assembly into functional units for neurotransmitter release. How cytoplasmically synthesized presynaptic active zone (AZ) proteins that organize SV release sites are transported and assembled is equally unclear. Here, we combine genome engineering in stem cell-derived neurons and genetically altered mice with proteomic, high-resolution imaging and systems biology approaches to identify the origin and composition of SV and AZ precursors, dissect the mechanisms of their axonal transport and integration into developing synapses and unravel the pathway that controls axonal transport and presynaptic assembly of newly made SV and AZ proteins to set synaptic weight. Our high risk/ high gain studies will yield groundbreaking insights into the mechanisms that mediate the formation, maintenance, and dynamic remodeling of the presynaptic compartment during development and thereby fill a crucial knowledge gap in neuroscience. Furthermore, they may pave the way for the future development of therapeutics to cure nerve injury or neurological disorders linked to synapse dysfunction.

LS-18. Synaptome architecture of the single neuron

Synapses participate in all our thoughts and actions and are damaged in over 100 genetic brain disorders. Synapses are the hallmark of brain complexity, being present in vast numbers and containing thousands of different proteins. Unravelling this complexity to get at the functional logic embedded within is a major challenge in neuroscience. We recently characterised excitatory synapse molecular diversity across the whole mammalian brain, revealing a remarkable 3D organisation of synapse types across the different regions – the ‘synaptome architecture’. This architecture is reorganised in genetic diseases, is important in structural and functional connectivity across the brain, and provides a mechanism for the storage and recall of information. But what of the fundamental, functional cellular building block of this

architecture – the single neuron and its dendritic tree? Crucially, very little is known about the distribution of synapse types on individual neurons and what this actually means for brain function. The overarching goal of SYNAPTOME is to define single-neuron synaptome architecture (SNSA). We will develop new genetic labelling and computational approaches to systematically map SNSA in the mouse brain. We will identify the SNSA of specific functional types of neurons and determine whether neurons share a canonical SNSA. We will reveal how the SNSA is built during development and how it is relevant to the connections between neurons and their physiological properties and functional output. We will ask if the SNSA can direct us to the specific synapses damaged in genetic disorders. These studies will uncover fundamental design principles inherent in the building blocks of the brain that link genome, proteome and synaptome with the architecture and function of individual neurons and their organisation into brain-wide networks. The new tools, resources and knowledge that SYNAPTOME will bring will have wide application in neuroscience and disease research.

LS-19. Genetics to understand cellular components of Alzheimer Disease pathogenesis

Alzheimer disease (AD) is a major health problem worldwide. New therapies require an accelerated translation of genetic information into mechanistic insights. Given limitations of rodent models, fully humanized models are needed to capture the complexity of the disease process. Human stem cells (iPS) provide great possibilities but are largely investigated in vitro with associated limitations. Many of the novel genetic risk factors for AD are expressed in microglia and astroglia, which remains an understudied population in this classically neuron-centric field. We propose here mouse-human chimeric mouse models to test the effects of AD-associated genetic risk factors on the phenotypes of transplanted microglia and astroglia derived from patients and from genomic engineered, isogenic stem cells. The cells will be followed during disease progression in brain of wild type and of mice developing Aβ- and Tau-pathology. Using single cell transcriptomics, a dynamic view of the cell states over time is generated. In a first arm of the project, we investigate how the genetic makeup of patient derived stem cells with high and low polygenic risk scores influences pathological cell states. In the second arm of the project, we generate inducible Crisper/CAS9 iPS isogenic cell lines to manipulate rapidly and specifically the expression of 4 selected AD associated genes linked to a putative cholesterol pathway but also affecting inflammation. These cell lines will be used also in the second phase of the project when validating hypotheses generated from the extensive bioinformatics analysis of the 600.000 single human cell profiles generated. We expect to identify and validate >5 novel drug targets in the astroglia-microglia axis of AD pathogenesis.

Our work provides humanized models for AD, an answer on how genetic makeup affects microglia and astroglia in an AD relevant context, and establishes a highly versatile platform to explore human genetics in human cells in vivo.

LS-20. Cognition in an Insect Brain

There is a common perception that larger brains mediate higher cognitive capacity. Social insects, however, demonstrate that sophisticated cognition is possible with miniature brains. Honeybees display higher-order learning such as categorization, non-linear discriminations, concept learning and numerosity, which are unique among insects. These capacities are mediated by a miniature brain with only 950 000 neurons. Despite extensive behavioral analyses, no study has attempted to elucidate the neural mechanisms underpinning the higher-order learning of bees. Our current breakthrough establishing virtual-reality protocols for tethered honeybees offers a unique opportunity to uncover the minimal circuits that mediate higher-order forms of cognitive processing in the brain of a behaving bee. We have recently shown that bees learn to solve elemental and non-elemental problems in this experimental context, which allows integrating behavioral, neurobiological and computational approaches to unravel the neural mechanisms underlying non-elemental learning in the honeybee. I will combine behavioral recordings of bees learning non-linear discriminations and relational rules in a virtual reality environment, with access to their brain via multi-photon calcium imaging and multielectrode recordings of neural populations. I will determine the neural circuits of elemental and non-elemental visual learning along the visual circuits of the bee brain, and the necessity and sufficiency of these circuits for these capacities via selective knockdown and rescuing via wavelength-selective multi-photon uncaging of neurotransmitters. Data will be fed into computational models to test hypotheses about minimal neural architectures for visual cognition, working towards whole-brain modeling. This project will expand the information available on the neurobiology of insect learning, and will provide the first integral characterization of the mechanisms underlying cognition in a miniature brain.

LS-21. The advent of the Iron Age in cell death

The recognition of distinct regulated cell death pathways presents tantalizing possibilities for gaining control over life and death decisions made by cells to both prevent age-dependent (neuro)degenerative diseases and to fight cancer. For decades, apoptosis has been considered as the sole form of regulated cell death, while others were deemed unregulated, necrotic. In this

context, pioneering work originating from my group enabled to establish “ferroptosis” as an iron-dependent cell death modality that is marked by the oxidative destruction of cellular membranes. Ferroptosis has sparked overwhelming interest in the last few years not only because it harbours many pharmacologically tractable nodes, but as it is likely induced only under pathological conditions, thus opening the unique opportunity for a broad therapeutic window of novel ferroptosis modulators. While some of the molecular players, metabolic contexts and respective small molecule inhibitors and inducers of ferroptosis have been recently described, pivotal questions have remained unanswered. In a holistic approach this project is conceived to tackle these fundamental questions by providing answers to (i) whether there are yet-unrecognized key ferroptosis nodes that may explain why certain cells are highly vulnerable to ferroptosis while others are not, (ii) the nature and subcellular compartment where the initial ferroptosis priming signal is being generated and (iii) why certain cells and tissues die by apoptosis while others succumb to ferroptosis. Successful implementation of the herein proposed aims will yield novel ferroptosis regulating genes as potential future drug targets, decipher and localize the death signal affording the rationale design of refined small molecule ferroptosis modulators and enable the precision-based treatment of patients suffering from early cell loss and tissue demise or cancer.

LS-22. MEtabolic Cell Reprogramming for the Recovery of Lost INsulin-Producing Cells

My group aims at fostering the regeneration of insulin-producing β-cells in the diabetic pancreas by promoting the reprogramming of other islet endocrine “non-β” cells. I will use mice and human islets to trigger the metabolic reprogramming of: i) peripheral organs, in order to reduce hyperglycemia, and ii) human islet non-β-cells, to induce their acquisition of insulin secretion. I developed transgenics to elicit total (>99%) or graded (5-90%) β-cell loss. These mice revealed that non-β-cells, which produce other hormones, can naturally switch to insulin production upon β-cell loss, and lead to diabetes recovery. My group recently showed that human non-β-cells, from healthy or diabetic donors, also display plasticity and can engage in regulated insulin secretion. What metabolic adaptations occur in peripheral organs in response to insulin deficiency, but without complications? Can metabolic reprogramming of peripheral organs, based on these adaptations, suffice to control glycemia? Can metabolic reprogramming change the identity of a cell? Natural recovery of euglycemia after β-cell loss is documented in mice. To know the mechanisms driving relief, my lab will characterize islet cell dynamics and circulating molecules (metabolites, RNA, peptides) after various degrees of β-cell loss. We will perform a full analysis of blood and peripheral organs in recovered mice, and an array of genetic

and pharmacological experiments modulating BAT mass and function to test its role in taming hyperglycemia. We will explore and define the metabolic differences between human β- and non-β-cells. Using monotypic "pseudoislets" we will do RNAseq, proteomics and metabolomics after exposure to glucose. We will quantify oxygen consumption, extracellular acidification and ATP production in response to nutrients and metabolic toxins. From this, we will genetically (CRIPR-Cas9) and chemically reprogram the metabolism of human non-β-cells to boost the expression of β-like genes.

LS-23. Imaging, characterizing and targeting metastatic niches in melanoma

Melanomas are the only tumors where lesions barely over one millimeter in depth can be at risk for metastasis. An increasing number of (epi)genetic alterations and mechanisms of immune evasion have been identified in this disease. Nevertheless, no molecular biomarker has been approved as a bona fide prognostic indicator. Progress in this field has been hampered by the paucity of models to visualize premetastatic niches in vivo, and monitor relapse after surgery. We have overcome these limitations by generating reporter mouse strains to "illuminate" premetastatic niches. Specifically, our "MetAlert" mice were designed for whole-body imaging of the aberrant expansion of the lymphatic vasculature, an early event that precedes metastasis. MetAlert, together with functional studies in human cells and histopathological validation in clinical biopsies, revealed the growth factor MIDKINE as a new melanoma-secreted prometastatic driver. We have now discovered roles of MDK as an immune suppressor, and identified a MDK-associated transcriptional profile that separates patients with a distinct expression of alarmins and bacterial response factors. Proteomic analyses revealed a set of additional factors secreted by aggressive melanoma cells, but their specific contribution to premetastatic niches is unclear. Here we will exploit our MetAlert and novel imaging reporters we have generated for a comprehensive spatio-temporal and functional analysis of premetastatic niches in vivo (including and beyond MDK). We will define how melanomas act "at a distance" before metastasis (Aim 1), and evade the immune system at different anatomical sites (Aim 2). Aim 3 will dissect the impact of the microenvironment, particularly via alarmins. Aim 4 will pursue the therapeutic targeting of metastatic niches (pre and post-surgery) with immunomodulators we discovered (and have led to clinical trials), and by targeting vulnerabilities that we found distinguish melanoma from other diseases.

LS-24. MECHANISMS BEHIND RESIDUAL DISEASE IN COLORECTAL CANCER and MODELLING OF THERAPIES THAT PREVENT RELAPSE

Disease relapse is a major complication in colorectal cancer (CRC). At the time of diagnosis, the majority of patients will present with locoregional disease that can be effectively resected by surgery. This intervention is sufficient to cure the primary disease in most cases. Yet, over the course of the following months or years, around 40% of the patients that underwent resection of the primary tumor with curative intention will relapse, generally in the form of metastatic disease. As these metastases eventually interfere with the function of vital organs such as the liver and lungs, patients that undergo relapse have poor prognosis. Recurrent cancer arises from clinically occult tumor cells that have disseminated to foreign organs (disseminated tumor cells or DTCs) before surgical removal of the primary CRC. Although the time window between surgery and relapse offers a good opportunity to prevent metastasis, current therapies are not effective at eliminating DTCs. Thus, there is an important unmet need to develop strategies to target residual disease. Advances in this area will benefit a large proportion of patients. Despite its clinical relevance, the study of residual disease in CRC has been largely neglected and the principles that govern the behavior of DTCs remain unknown. The main reason for this important knowledge gap is that residual tumor cells are difficult to study in patients, as they remain clinically occult. We have recently generated a unique set of compound mutant mice and organoids that reproduce key features of human metastatic CRC. We propose to leverage these new models to study the biology of residual disease. We will characterize the features of DTCs using single cell transcriptional profiling, analyze the influence of driver mutations on DTC behavior, explore mechanisms of immune evasion during the latency phase, and model DTC latency in vivo and in vitro. Our ultimate goal is to design therapies that prevent disease relapse in CRC.

LS-25. Targeting Shelterin Proteins in Cancer

Telomeres are protective structures at the chromosome ends essential for genome stability. Telomere biology is intricately linked with human cancer. Most cancer cells reactivate telomerase to avoid telomere loss associated to cell division. Targeting telomerase inhibition in cancer has shown very limited efficacy, alternative or additional mechanisms of telomere maintenance are thus at play in cancer. Recent evidence shows that components of the telomere-protecting shelterin complex are mutated in cancer. Shelterin prevents chromosome fusions, impedes persistent DNA damage response at telomeres and regulates telomerase activity. We

were first in describing shelterin mutations in cancer and pioneered the idea of targeting shelterin as an anticancer strategy to induce length-idependent telomere damage. We also found that key cancer pathways regulate shelterin function throughout post-transcriptional modifications. Developing new therapeutic approaches based on targeting shelterin is hampered by lack of mouse models and incomplete understanding of which underlying mechanisms mutations in shelterin drive tumour development. We strive to establish a comprehensive set of tools, to enable us to conduct a fundamental and far-reaching experimental programme on the role of shelterin in cancer. Our specific aims are to i) generate knock-in mice to understand the role of POT1 shelterin mutations found in cancer and develop personalized therapeutic strategies based on these alterations, ii) generate knock-in mice to understand the role of post-translational modifications of the TRF1 shelterin by several cancer pathways for the identification of new cancer targets, and iii) dissect the potential role of TRF1 in cancer stem cells. We expect to block the ability of cancer cells to divide indefinitely and effectively impair cancer growth. Our research programme will reveal the role of two fundamental aspects of biology, telomere capping and chromosomal stability, in cancer.

LS-26. Tracking and Targeting Tumor States at single-cell resolution in real time in vivo

It is now widely recognized that within a tumor, not all cancer cells are alike and different tumor states (TS) exist. This process is known as tumor heterogeneity. Some cancer cells actively proliferate, while others differentiate, migrate and give rise to metastasis, or enter in a dormant state and resist to chemotherapy. The identification of distinct TS and the mechanisms that regulate their identities and functions is critical for our understanding of tumor heterogeneity. The different TS can acquire distinct phenotypes responsible for tumor progression, metastasis, and therapy resistance. In this project, using multidisciplinary approaches that combine single-cell lineage tracing, single-cell genomics, epigenomics and transcriptomics together with pharmacological treatment and genetic perturbations, we will define in a comprehensive and integrated manner the identities and functions of distinct TS at single-cell resolution in squamous cell carcinoma (SCC). Then, we will develop new genetically engineered tumor models expressing different fluorescent proteins to visualize the dynamics of TS in real time in vivo using intravital microscopy. Moreover, we will assess the roles of the identified TS by lineage ablation and identify the intrinsic and extrinsic mechanisms that regulate their transitions and functions, which will help to define new tumor vulnerabilities and provide new therapeutic opportunities.

LS-27. Breaking borders, Functional genetic screens of structural regulatory DNA elements

The human genome carries genetic information in two distinct forms: Transcribed genes and regulatory DNA elements (rDEs). rDEs control the magnitude and pattern of gene expression, and are indispensable for organismal development and cellular homeostasis. Nevertheless, while large-scale functional genetic screens greatly advanced our knowledge in studying mammalian genes, such tools to study rDEs were lacking, impeding scientific progress. Interestingly, recent advance in genome editing technologies has not only expanded the available screening toolbox to examine genes, but also opened up novel opportunities in studying rDEs. We distinguish two types of rDEs: Transcriptional rDEs that recruit transcription factors to enhancers, and structural rDEs that maintain chromatin 3D structure to insulate transcriptional activities, a feature postulated to be essential for gene expression regulation by enhancers. Recently, we developed a CRISPR strategy to target enhancers. We showed its scalability and effectivity in identifying potential oncogenic and tumour-suppressive enhancers. Here, we will exploit this line of research and develop novel strategies to target structural rDEs (e.g. insulators). By setting up functional genetic screens, we will identify key players in cell proliferation, differentiation, and survival, which are related to cancer development, metastasis induction, and acquired therapy resistance. We will validate key insulators and decipher underlying mechanisms of action that control phenotypes. In a parallel approach, we will analyse whole genome sequencing datasets of cancer to identify and characterize genetic aberrations occurring in the identified regions. Altogether, the outlined research plan forms a natural extension of our successful functional approaches to study gene regulation. Our results will setup the foundation to better understand principles of chromatin architecture in gene expression regulation in development and cancer.

LS-28. Targeting endothelial barriers to combat disease

Tissue homeostasis requires coordinated barrier function in blood and lymphatic vessels. Opening of junctions between endothelial cells (ECs) lining blood vessels leads to tissue fluid accumulation that is drained by lymphatic vessels. A pathological increase in blood vessel permeability or lack or malfunction of lymphatic vessels leads to edema and associated defects in macromolecule and immune cell clearance. Unbalanced barrier function between blood and lymphatic vessels contributes to neurodegeneration, chronic inflammation, and cardiovascular disease. In this proposal, we seek to gain mechanistic understanding into coordination of barrier

function between blood and lymphatic vessels, how this process is altered in disease models and how it can be manipulated for therapeutic purposes. We will focus on two critical barriers with diametrically opposing functions, the blood-brain barrier (BBB) and the lymphatic capillary barrier (LCB). ECs of the BBB form very tight junctions that restrict paracellular access to the brain. In contrast, open junctions of the LCB ensure uptake of extravasated fluid, macromolecules and immune cells, as well as lipid in the gut. We have identified novel effectors of BBB and LCB junctions and will determine their role in adult homeostasis and in disease models. Mouse genetic gain and loss of function approaches in combination with histological, ultrastructural, functional and molecular analysis will determine mechanisms underlying formation of tissue specific EC barriers. Deliverables include in vivo validated targets that could be used for i) opening the BBB on demand for drug delivery into the brain, and ii) to lower plasma lipid uptake via interfering with the LCB, with implications for prevention of obesity, cardiovascular disease and inflammation. These pioneering studies promise to open up new opportunities for research and treatment of neurovascular and cardiovascular disease.

LS-29. Cross-talk between platelets and immunity - implications for host homeostasis and defense

The overall aim of the IMMUNOTHROMBOSIS project is to clarify the mechanisms underlying the recently identified synergism between thrombosis and inflammation. Thrombus formation and inflammation are vital host responses that ensure homeostasis, but can also drive cardiovascular disease, including myocardial infarction and stroke, the major causes of death in Europe. My group and others discovered, that thrombosis and inflammation are not to be considered separate processes. They are tightly interrelated and synergize in immune defence, but also in inflammatory and thrombotic diseases in a process we termed immunothrombosis. Targeting this synergism has great potential to identify innovative and unconventional strategies to more specifically prevent undesired activation of thrombotic and inflammatory pathways. However, this requires a deeper mechanistic understanding of immunothrombosis. I recently identified two ground-breaking novel immunothrombotic principles: I discovered that platelets have the ability to migrate autonomously, which assists immune cells in fighting pathogens. Further, I revealed that immune cells play a central role in controlling the production of platelets from their megakaryocyte precursors. The physiological and pathophysiological relevance of both processes is unclear. This is the starting point and focus of the IMMUNOTHROMBOSIS project. My aim is to define how platelets use their ability to migrate to support immune cells in protection of vascular integrity (objective 1) and to identify the

contribution of platelet migration to different cardiovascular diseases involving immunothrombotic tissue damage (objective 2). Finally, I will clarify how inflammatory responses feedback to the production of thrombotic effectors and dissect inflammatory mechanisms that control platelet production (objective 3). IMMUNOTHROMBOSIS will identify new options for specific prevention or treatment of thrombotic and inflammatory cardiovascular diseases.

LS-30. Nucleolar regulation of longevity

Research over the last few decades has revealed that animal life span is malleable and regulated by conserved metabolic signaling pathways, including reduced insulin/IGF signaling, mTOR, mitochondrial function, dietary restriction, and signals from the reproductive system. Whether these various pathways converge on common processes, however, has remained elusive. We recently discovered the nucleolus to be a crucial focal point of regulation in all these pathways. The nucleolus is a subnuclear organelle dedicated to rRNA production and ribogenesis, but also controls assembly of other ribonucleoprotein complexes including spliceosomes, signal recognition particle, small RNA processing, stress granules, and responds to growth and stress signaling. Remarkably we found that small nucleoli are a cellular hallmark of longevity in diverse species, and a correlate of metabolic health in humans. At the molecular level, long-lived animals show reduced levels of the nucleolar ribosomal RNA methylase, fibrillarin (FIB-1), and knockdown of C. elegans FIB-1 reduces nucleolar size, extends life span, and enhances innate immunity. Conversely, knockout of NCL-1/TRIM2 expands nucleolar size, suppresses life extension of major longevity pathways, and renders animals pathogen sensitive, revealing key regulators of nucleolargenesis, immunity and longevity. Here I propose to (Aim 1) clarify the mechanism of action of NCL-1, FIB-1 and interacting molecules (2) perform novel genetic screens for nucleolargenesis in C. elegans (3) uncover global transcriptomic and proteomic changes induced by NCL-1 and FIB-1 and survey several candidate nucleolar processes in regulating longevity and immunity (4) probe NCL-1/TRIM2 regulation of longevity in the short-lived killifish, Notobranchius furzeri, and develop nucleolar biomarkers of metabolic health in humans. These groundbreaking studies should illuminate how conserved signaling pathways work through the nucleolus to regulate health and life span.

Physical sciences & engineering (PE) sub-corpus

PE-1. Attosecond physics, free electron quantum optics, photon generation and radiation biology with the accelerator on a photonic chip

Resting on our demonstration of laser-driven nanophotonics-based particle acceleration, we propose to build a miniature particle accelerator on a photonic chip, comprising high gradient acceleration and fully optical field-based electron control. The resulting electron beam has outstanding space-time properties: It is bunched on sub-femtosecond timescales, is nanometres wide and coherent. We aim at utilizing this new form of all-optical free electron control in a broad research program with five exciting objectives: (1) Build a 5 MeV accelerator on a photonic chip in a shoebox-sized vessel, (2) Perform ultrafast diffraction with attosecond and even zeptosecond electron pulses, (3) Generate photons on chip at various wavelengths (IR to x-ray), (4) Couple quantum-coherently electron wavepackets and light in multiple interaction zones, and (5) Conduct radiobiological experiments, akin to the new FLASH radiotherapy and Microbeam cell treat-ment. AccelOnChip will enable five science objectives potentially shifting the horizons of today's knowledge and capabilities around ultrafast electron imaging, photon generation, (quantum) electron-light coupling, and radiotherapy dramatically. Moreover, AccelOnChip promises to democratize accelerators: the accelerator on a chip will be based on inexpensive nanofabrication technology. We foresee that every university lab can have access to particle and light sources, today only accessible at large facilities. Last, AccelOnChip will take decisive steps towards an ultracompact electron beam radiation device to be put into the tip of a catheter, a potentially disruptive radiation therapy device facilitating new treatment forms. AccelOnChip is a cross-disciplinary high risk/high return project combining and benefiting nanophotonics, accelerator science, ultra-fast physics, materials science, coherent light-matter coupling, light generation, and radiology - and is based on my group's unique expertise acquired in recent years.

PE-2. Scattering Amplitudes for Gravitational Wave Theory

Four years ago, the LIGO/Virgo observation of a black-hole binary merger heralded the dawn of gravitational-wave astronomy. The promise of future observations calls for an invigorated effort to underpin the theoretical framework and supply the predictions needed for detecting future signals and exploiting them for astronomical and astrophysical studies. Ampl2Einstein will take ideas and techniques from recent years' dramatic advances in Quantum Scattering Amplitudes, creating new tools for taking their classical limits and using it for gravitational physics. The powerful `square root' relation between gravity and a generalization of electrodynamics known as Yang--Mills theory will play a key role in making this route simpler than direct classical calculation. We will transfer these ideas to classical General Relativity to compute new perturbative orders, spin-dependent observables, and the dependence on the

internal structure of merging objects. We will exploit symmetries and structure we find in order to extrapolate to even higher orders in the gravitational theory. We will make such calculations vastly simpler, pushing the known frontier much further in perturbation theory and in complexity of observables. These advances will give rise to a new generation of gravitational-wave templates, dramatically extending the observing power of detectors. They will allow observers to see weaker signals and will be key to resolving long-standing puzzles about the internal structure of neutron stars. We will apply novel technologies developed for scattering amplitudes to bound-state calculations in both quantum and classical theory. Our research will also lead to a deeper understanding of the classical limit of quantum field theory, relevant to gravitational-wave observations and beyond. The transfer of ideas to the new domain of General Relativity will dramatically enhance our ability to reveal new physics encoded in the subtlest of gravitational-wave signals.

PE-3. Biomedical Applications of Radioactive ion Beams

Cancer remains one of the main causes of death worldwide. In 2018, >50% cancer patients in Europe underwent radiotherapy. While over 80% were treated using high-energy X-rays, the number of patients receiving accelerated protons or heavy ions (charged particle therapy: CPT) is rapidly growing, with nearly 200,000 patients treated up till now. Although CPT offers a better depth-dose distribution compared to common X-ray based techniques, range uncertainty and poor image guidance still limit its application. Improving accuracy is key to broadening the applicability of CPT. In BARB, we will open a new paradigm in the clinical use of CPT by using high-intensity radioactive ion beams (RIB), produced at GSI/FAIR-phase-0 in Darmstadt, for simultaneous treatment and visualization. This will reduce range uncertainty and extend the applicability of CPT to treatment of small lesions (e.g. metastasis and heart ventricles) with unprecedented precision. The Facility for Antiprotons and Ion Research (FAIR) is currently under construction at GSI. RIB are one of the main tools for basic nuclear physics studies in the new facility. As part of the ongoing FAIR-phase-0, an intensity upgrade will increase the light ion currents in the existing SIS18 synchrotron. Within this project BARB, we will study four b+ emitters (10,11C, and 14,15O) and build an innovative hybrid detector for online positron emission tomography (PET) and g-ray imaging. This novel detector will acquire both prompt g-rays during the beam-on phase of the pulsed synchrotron beam delivery, and the delayed emission from b+ annihilation during the pulse intervals. The technique will be further validated in vivo by applying it to treatment of small tumors in a mouse model. BARB will exploit the potential of the Bragg peak in medicine. The project will tweak RIB production in

nuclear physics and validate the therapeutic potential of RIB therapy in vivo by empowering simultaneous treatment and visualization.

PE-4. Flavour Anomalies with advanced particle Identification Methods

In the proposed research, precision measurements of rare processes involving heavy quarks and leptons will be used to search for new phenomena beyond the Standard Model, popularly known as New Physics. This research at the intensity frontier is complementary to searches at the highest achievable energies carried out at the LHC proton-proton collider. Indications of very interesting discrepancies have recently been observed by three experiments (LHCb, BaBar, and Belle) between their results and predictions of the Standard Model in certain classes of decays of B mesons, which involve leptons in the final state. The proposed project will address these issues by using large event samples collected with the Belle II detector at a new electron-positron collider, SuperKEKB. By investigating a broad range of selected rare decays of B and D, the project will attempt to provide a definite answer on the violation of Lepton Flavour Universality, one of the cornerstones of our current understanding of the interactions among the elementary particles. Based on the results of these studies, the final stages of the project will be devoted to possible explanations and to studies of transitions that would be based on related new physics phenomena. Within the proposed research programme, novel, highly advanced identification methods for charged particles will also be developed. They will be of crucial importance to suppress backgrounds arising from other, much more abundant decays in measurements of rare processes where the sensitivity to a possible contribution of New Physics is largest. The proposed research will strongly benefit from the fact that the same group that contributed substantially to the physics programme, concept, design, and construction of the detector, will also carry out the development of novel analysis methods, their calibration and optimization for individual reactions.

PE-5. Probing r-process nucleosynthesis through its electromagnetic signatures

The lightest chemical elements –Hydrogen and Helium– were created about a minute after the Big Bang. Elements up to Iron are forged by fusion reactions in stars. Heavy elements between Iron and Uranium are produced by a sequence of neutron captures and beta-decays known as rapid neutron capture or r process. The freshly synthesized r-process elements undergo radioactive decay through various channels depositing energy in the ejecta that powers an optical/infrared transient called “kilonova” whose basic properties like luminosity and its

dependence on ejecta mass, velocity, radioactive energy input, and atomic opacities I contributed to determine for the first time. Our predictions have been dramatically confirmed by the observation of a kilonova electromagnetic transient associated with the gravitational wave signal GW170817 providing the first direct indication that r-process elements are produced in neutron-star mergers. Additional events are expected to be detected in the following years, representing a complete change of paradigm in r-process research as for the first time we will be confronted with direct observational data. To fully exploit such opportunity it is fundamental to combine an improved description of exotic neutron-rich nuclei involved in the r-process with sophisticated astrophysical simulations to provide accurate prediction of r-process nucleosynthesis yields and their electromagnetic signals to be confronted with observational data. Based on my broad knowledge and expertise in all the relevant areas, and the unique experimental capabilities of the GSI/FAIR facility, I am in prime position to advance our understanding of r-process nucleosynthesis and determine the contribution of mergers to the chemical enrichment of the galaxy in heavy elements.

PE-6. Monolithic Multi-Junction Picosecond Avalanche Detector for future physics experiments and applications

Particle-physics, space research and several other fields of basic and applied science necessitate the production of thin sensors capable to provide excellent position and time resolution at the same time. The diode structure of present silicon pixel sensors strongly penalises the enormous potential of silicon-based time measurement: the ~30 ps intrinsic limit of diodes was already reached in sensors with internal gain with pad sizes of 1 mm2. Therefore, new ideas are needed to improve by another order of magnitude and reach the picosecond level. This project introduces a novel silicon-sensor structure devised to overcome the intrinsic limits of present sensors and simultaneously provide picosecond timing and high spatial resolution in a monolithic implementation. This goal is achieved by the introduction of a fully depleted multi-junction. The remarkable performance of this new sensor, combined with the simplified assembly process and reduced production cost offered by the monolithic implementation in standard CMOS processes, represent the required breakthrough. In addition to the novel multi-junction sensor, the cornerstones of the project are the low-noise very-fast SiGe HBT frontend and the patented TDC with robust synchronisation method that the PI has already produced in preliminary versions. The monolithic detector proposed here will offer a sustainable solution for the next generation of experiments at hadron colliders, in nuclear physics and for space-borne experiments in cosmic-ray physics and solar physics. Besides the primary goal of basic

science, it will represent an extraordinary enabling technology for the large spectrum of high-tech applications that benefits of picosecond-level Time-Of-Flight measurements. The innovative monolithic detector introduced here will also offer a starting point for further progress in the field of light detection. European industrial partners have been contacted for commercial exploitation of the detector.

PE-7. Nuclear rEaCTions At storage Rings

Obtaining reliable cross sections for neutron-induced reactions on unstable nuclei is a highly important task and a major challenge. These data are essential for nuclear astrophysics -since most of the heavy elements in the Universe are produced by neutron-induced reactions in stars- and for applications in nuclear technology. However, their measurement is very complicated as both projectile and target are radioactive. The most promising way to infer these cross sections is to use surrogate reactions in inverse kinematics, where the nucleus formed in the neutron-induced reaction of interest is produced by a reaction involving a radioactive heavy-ion beam and a stable, light target nucleus. The decay probabilities (for fission, neutron and gamma-ray emission) of the nucleus produced by the surrogate reaction provide precious information to constrain models and enable much more accurate predictions of the desired neutron cross sections. Yet, the use of surrogate reactions is hampered by the numerous long-standing target issues. I propose to solve them by combining surrogate reactions with the unique possibilities at ion storage rings. In a storage ring heavy radioactive ions revolve at high frequency passing repeatedly through an electron cooler, which will greatly improve the beam quality and restore it after each passage of the beam through the internal gas-jet serving as ultra-thin, windowless target. This way, decay probabilities can be measured with unrivaled accuracy. NECTAR aims to develop a detection system based on cutting-edge technology and a new method to measure accurate decay probabilities of radioactive nuclei at the CRYRING storage ring of the GSI/FAIR facility. The extreme vacuum conditions of the ring put severe constraints on the detection setup. I propose original, even revolutionary options to overcome these issues like the use of solar cells. Thus, NECTAR will be the seed of a new generation of nuclear-reaction experiments with unstable beams.

PE-8. Nuclear Theory from First Principles

Nuclear physics aims at understanding the emergence and properties of complex structures like atomic nuclei from QCD, the underlying theory of the strong interaction, and addresses some

of the Big Science Questions including the origin of the elements, the limits of nuclear stability, searches for physics beyond the Standard Model and physics of neutron stars. Answering these questions requires a reliable theoretical approach to nuclear structure and reactions. Chiral effective field theory (EFT) combined with ab initio many-body methods provides an efficient and well-founded framework, and a major effort is needed to push the precision of nuclear forces and develop an efficient matching with the emerging lattice QCD results. Recently, the PI and his group made significant breakthroughs in the two-nucleon (2N) sector by developing chiral EFT interactions which are more precise than any other potentials and, for the first time, qualify to be regarded as partial wave analysis (PWA). This shows that chiral EFT can, without any compromises on rigor and consistency, be advanced to a precision tool. While the 2N sector can be considered as solved, three-nucleon (3N) scattering data could so far not be described showing that the simplest nuclear system beyond the 2N one is not understood. Given this success in the 2N sector, I propose to perform for the first time a PWA of 3N scattering and to determine the Hamiltonian complete up through fifth order. The project aims at solving the long-standing 3N force challenge and development of accurate, state-of-the-art nuclear forces determined solely by the chiral symmetry of QCD and few-nucleon data. The resulting Hamiltonian will be used in large-scale ab initio calculations of nuclear structure and reactions. We will also develop an efficient interface between lattice QCD and chiral EFT. If successful, these studies will establish a rigorous, fully microscopic approach to nuclear physics firmly rooted in QCD.

PE-9. Photon-photon and spin-spin Entanglement using Diamond-based impurity Elements: Silicon, Tin And Lead

Quantum technologies promise revolutionary capabilities in processing information and transmitting with security over a network certified by the principles of quantum physics. The key hardware element of a quantum network is the ‘node’, where a stationary qubit cluster perform primitive processes and communicate with other nodes by exchanging flying qubits. The interfacing between the stationary qubit cluster and the flying qubits is realised by a special ‘broker qubit’. Today, the most competitive candidates for flying and stationary qubits are photons and diamond spins, respectively, and this opportunity is being pursued worldwide. A specific emitter in diamond, the Nitrogen Vacancy (NV), has enabled landmark demonstrations of basic quantum building blocks, but faces fundamental challenges on reaching the optical qualities required to scale up. PEDESTAL offers an efficiency boost to the NV while building on key advances in diamond technology. Our goal is to create a quantum node hardware

prototype with characteristics required to sustain a multi-purpose quantum network capable of implementing simultaneous quantum communications and computing. PEDESTAL will develop a demonstrator quantum node based on diamond group-4 spins, which offer specifications outperforming others. Benchmarking against the known silicon-vacancy (SiV) centre, our workhorse will be the tin-vacancy (SnV) centre, which we have shown to have outstanding qualities satisfying the requirements for a quantum node. In parallel, we will develop to maturity the less-known but highly promising lead-vacancy (PbV) centre which can operate with more feasible conditions and develop a novel technique to control spins. Our objectives include creating multi-spin and multi-photon entangled states as resource and will complete its key objectives with the demonstration of distributed three-spin entanglement, culminating in the experimental demonstration of a high-fidelity, high-bandwidth multi-node quantum network.

PE-10. Quantum Physics with Attosecond Pulses

This project lies at the crossing of attosecond science, photoionization of atoms and molecules and quantum optics. Progress in the performances of the attosecond sources, in particular regarding repetition rate, now enables us to perform photoionization studies of atoms and molecules using advanced coincidence/three dimensional momentum techniques. Adding an additional dimension, the phase, which is accessible by attosecond interferometric techniques, we will able to follow in time the quantum properties of the studied processes. The aim of the present application is to perform quantum optics experiments, not with photons as in conventional quantum optics, but with electron wave-packets created by absorption of attosecond light pulses. Our objectives are - to characterize and study in the time domain the quantum coherence of attosecond electron wavepackets, - to control quantum interferences of electron wavepackets using a small number of attosecond pulses and - to create and follow in time entangled two-electron attosecond wavepackets. The experiments will use advanced laser systems, attosecond sources and electron detectors. A unique 200-kHz repetition rate laser system based on optical parametric chirped pulse amplification technology, combined with an efficient attosecond source and a three-dimensional momentum electron detector will open the door to attosecond experiments where the kinematics of the light-matter interaction can be recorded. The success in achieving the above objectives will not only lead to a major leap forward in attosecond science and atomic and molecular physics in general; it might shed new lights in fundamental quantum physics, given the originality of the studied systems, attosecond

electron wave packets and the versatility of the tools, providing four dimensional information (momentum and time) for multiple particles.

PE-11. Nanoscale Aromaticity and Supramolecular Electronic Materials

ARO-MAT will target emergent cooperative electronic and magnetic phenomena in molecules with dimensions of 5–25 nm (i.e. as big as many proteins). The project will develop supramolecular architectures with large pi-systems and well-defined geometries, in which the frontier orbitals coherently delocalize charge over the whole nanostructure. Aromaticity is a key emergent phenomenon; it can be defined as the ability of a cyclic molecule to sustain a ring current when placed in a magnetic field. Until recently, it was thought that aromaticity is restricted to small molecules, with circuits of less than about 22 pi-electrons. Anderson has shown that circuits of more than 160 pi-electrons (circumference > 15 nm) can exhibit strong aromatic ring currents. Testing even larger rings will elucidate the link between aromaticity and the persistent currents found in non-molecular mesoscopic rings (diameter 50–500 nm). ARO-MAT will explore the effects of molecular size and topology on nanoscale aromaticity. Other emergent phenomena to be addressed include the formation of open-shell singlet polyradical ground states, magnetic bistability in systems with many paramagnetic metal centers, and the control of charge transport through single-molecule devices by quantum interference. This multidisciplinary project combines organic synthesis, supramolecular chemistry, theory, electronic structure calculations, NMR and EPR spectroscopy, magnetochemistry, molecular electronics and low-temperature charge transport experiments. The core objective is to create low band gap materials with unprecedented electronic and magnetic properties, and to understand the structure-property relationships governing the behavior of these new materials. Most of the target structures are based on metalloporphyrins because of their redox activity, stability, structural versatility, suitability for template-directed synthesis and ability to position multiple strongly coupled paramagnetic metal centers.

PE-12. Designer enzymes featuring unnatural amino acids as catalytic residue

Biocatalysis is a key component of the transition towards a more sustainable and “greener” chemistry. Surprisingly, natural enzymes use only a relatively small section of “reaction space”, that is, only limited number of reaction classes. This in marked contrast to the vast reaction space available to the synthetic chemist. Therefore, it is highly desirable to have enzymes available for the catalysis of these abiological reactions. With the advent of robust expanded

genetic code methodologies, it is now feasible to introduce a wide variety of unnatural amino acids into proteins. We envision that the time has come to use this breakthrough technology to create enzymes that contain abiological reactive groups as catalytic residue, for the catalysis of reactions that are not possible using canonical amino acids only. The global aim of this project is the creation and application of designer enzymes with genetically encoded unnatural amino acids as catalytic residue for novel and new-to-nature catalysis. The following research objectives are key to achieving the overall aim: 1. Achieving incorporation of unnatural amino acids containing organocatalytic side chains in proteins. 2. Creation of a library of novel designer enzymes containing unnatural amino acids as catalytic residue. 3. Application of these designer enzymes in catalysis of important reactions that have no equivalent in nature. 4. Directed evolution of designer enzymes featuring unnatural amino acids as catalytic residue. 5. Application of designer enzymes containing UAAs as catalytic residue in biocatalytic cascades. This highly ambitious project combines frontier chemical and biochemical research and will deliver completely new classes of enzymes that can access new and previously unexplored parts of biocatalytic "reaction space". In this way, this project will contribute to achieving the important societal goal of achieving greener and more sustainable approaches to chemical synthesis.

PE-13. Artificial Translation with Dynamic Foldamers: Relaying Encoded Messages into Chemical Function

We propose to apply the power of synthetic chemistry to a new challenge in synthetic biomimicry: the translation of encoded information into molecular function. We propose to design and build switchable synthetic molecules that are capable of communicating and processing information. This ambitious aim will be achieved through new classes of extended dynamic molecules that respond to their environment by changing shape, principally by invertase polarity/directionality. They will receive, communicate, amplify, transmit, and process information encoded in their molecular conformation and orientation. New analystic methods will be developed to explore their kinetics and thermodynamics. Characterized by a high level of intramolecular structural organization, they will participate in strong, selective mutual interactions, allowing them to process information through intramolecular and intermolecular interactions in simple and complex mixtures, both solution and in the membrane phase. These chemical systems will be able to extract information from their environment (the presence of a specific metal or organic molecule, a genetically encoded message, pH, or irradiation at a specific wavelength) and process it into chemical function. Life takes

information in the form of bond polarity encoded in base pairs and translates it into biochemical function in the form of protein structure, and our synthetic structures will likewise translate molecular polarity into function by using new classes of 'promiscuous' Watson-Crick-like base-pairs, able to switch between alternative hydrogen-bond polarities. Applications for these synthetic communication systems will ultimately see them embedded into cell membranes, allowing the selective control of function by communicating into the interior of both artificial vesicles and living cells.

PE-14. Earth-Abundant Metals with Exclusively Achiral Ligands for Sustainable Chiral-at-Metal Catalysis

Asymmetric catalysis relies on the design of chiral catalysts and is dedicated to the economical generation of non-racemic chiral compounds, which are building blocks for the production of drugs, agricultural chemicals, flavors, fragrances, and materials. Chiral transition metal complexes constitute an important class of chiral catalysts and are typically synthesized by combining metal salts or organometallic precursors with chiral ligands. A neglected approach follows a different direction and exploits the generation of metal-centered chirality in the course of the assembly of achiral ligands around a central metal. Our group has pioneered the general use of such chiral-at-metal catalysts from noble metals, with the metal center both serving as the exclusive stereogenic center and at the same time acting as the reactive center for catalysis. The design of reactive chiral-at-metal catalysts based on earth-abundant metals, which have economical and environmental benefits, is the focus of this proposal. The design strategy appeals for its combination of sustainability (earth-abundant metals) and simplicity (achiral ligands). Furthermore, without the requirement for chiral motifs in the ligand sphere, untapped opportunities emerge for the design of chiral 3d metal complexes with distinct electronic properties and unique architectures. This unexplored chemical space for chiral catalysts will be applied to the challenging enantioselective functionalization of C(sp3)-H bonds with inexpensive and sustainable 3d metal catalysts. The implementation of chiral-at-metal catalysts from earth-abundant metals will rely on taming the high lability of coordinative bonds of 3d metals to warrant a satisfactory configuration stability. This will be addressed by exploiting the chelate effect of tailored multidentate ligands in combination with strong-field ligands and attractive weak interactions between coordinated ligands.

PE-15. Enantioselective C-H Oxidation Guided by Rational Catalyst Design

Chemo- and enantioselective oxidation of aliphatic C-H bonds is a cornerstone reaction in metabolism. The ubiquitous presence of multiple and diverse C-H bonds in organic molecules is used by oxidative enzymes to deliver functionality and chirality to metabolite precursors, rapidly creating product diversity. Despite its huge potential in organic synthesis, non-enzymatic enantioselective C-H oxidation of aliphatic sites remains inaccessible and has never been incorporated in synthesis. Harnessing the power of this reaction will open straightforward, yet currently inaccessible, paths in synthetic planning. However, realization of this goal requires conceptual breakthroughs in order to chemo-, regio- and stereo-selectively create a C-O bond from a non-activated alkyl C-H bond, even in the presence of a priori more reactive groups. In this project, chemo-, and site-selective asymmetric aliphatic oxidation is targeted by taking advantage of; a) stereoretentive enzyme-like metal-based C-H oxidations performed by small molecule manganese catalysts, devised as minimalistic hydroxylases, and b) polarity reversal exerted by fluorinated alcohol solvents in electron-rich functional groups, which enable chemoselective C-H hydroxylation of densely functionalized molecules. Desymmetrization via enantioselective C-H oxidation is devised as a powerful type of reaction that will create multiple chiral centers in a single step. Building on the rich chemical diversity and modular architecture of aminopyridine manganese complexes, rapid elaboration of libraries of catalysts is targeted. Rational manipulation of steric, electronic, directing effects and supramolecular substrate recognition factors guided by multiple parametrization analyses will be employed for directing evolution in catalyst design. This project will provide the catalysts and their use in paradigmatic reactions in order to establish enantioselective C-H oxidation as a reliable tool in organic synthesis.

PE-16. Escaping from Flatland by “de novo” Catalytic Decarboxylation Techniques

Although cross-coupling reactions have become one of the pillars of modern chemical synthesis, the ability to forge sp3–sp3 bonds with improved flexibility, practicality, predictable site-selectivity, preparative utility, stereocontrol and with nearly zero-generation of waste has eluded chemists for decades, remaining a major challenge and an uncharted cartography in catalytic endeavours. The successful realization of this goal will represent a paradigm shift from the standard logic of organic synthesis in both basic and applied research, as increasing the number of sp3-hybridized carbon atoms has become a necessary goal in the drug discovery pipeline. NOVOFLAT offers a pioneering approach for forging sp3–sp3 linkages via a triple catalytic cascade that enables an unprecedented intramolecular decarboxylation of simple and available carboxylic acid esters with CO2 as the sole byproduct. As ester derivatives simply

derive from naturally-occurring carboxylic acids and alcohols, this proposal will allow to rapidly access sp3–sp3 linkages with different electronic and steric requirements, thus providing an invaluable opportunity to streamline the discovery of important architectures with applications across the molecular sciences. Preliminary results demonstrate the feasibility to provide "a la carte" predictable tool that chemists could use to control the site where the sp3–sp3 bond-formation takes place in both aliphatic and cyclic frameworks, even at remote sp3 sites. In addition, our general principle offers an unrecognized opportunity to simultaneously construct sp3–sp3 linkages and control the stereochemistry at remote sp3 sites. In this manner, NOVOFLAT will not only provide new dogmas in retrosynthetic analysis by fundamentally altering the way sp3–sp3 bonds are made, but also open new vistas in "chain-walking" reactions, as the incorporation of chirality throughout the alkyl side-chain constitutes "terra incognita" in these technologies.

PE-17. Chemical Space for Antimicrobials on a Peptide Basis

Multidrug resistant (MDR) bacteria represent a global public health threat against which new drugs are urgently needed. Antimicrobial peptides (AMPs), mostly derived from naturally occurring linear or cyclic peptides, can contribute to solving the problem. AMPs are already in clinical use, do not easily lead to resistance, and can rely on a strong manufacturing sector and established protocols for clinical development. However, most AMPs are degraded by proteases and have poor pharmacokinetics. SPACE4AMPS aims to identify new AMPs with diverse peptide chain topologies and building blocks and with the following characteristics: i) Broad activity spectrum, ii) High activity, iii) Low probability for induced resistance, iv) Low proteolysis, v) Better pharmacokinetics. To reach its goal SPACE4AMPS will create computational tools to explore the extremely vast chemical space of large molecules such as peptides and natural products, which now lies within reach of the latest computer hardware developments. To better understand antimicrobial drugs, we will design a molecular fingerprint relating antimicrobial activity to molecular structure and use it to draw a tree-map of the antimicrobial chemical space. We will enrich this map with new compounds from generative models using neural networks. To identify new AMPs, we will use a genetic algorithm carrying out cycles of molecule generation and similarity calculations to select cyclic peptides and peptide dendrimers including lipidated, peptoid (N-alkyl glycines) and N-methylated residues, synthesize and test these molecules against MDR bacteria, fungi and parasites, screen actives for toxicity, and study their structure and mode of action. By its ground-breaking and unprecedented computational/synthetic/biological approach, SPACE4AMPS can help solve the

antibiotics crisis, revolutionize knowledge on antimicrobial compounds, and create new methods enabling computer-aided drug discovery for large molecules.

PE-18. SYNergistic SORBents

This is the “Age of Gas”; disruptive new technologies must develop around the use of gases as fuels, therapies or feedstock chemicals. Specifically, new approaches to gas storage (transportation and delivery) and purification (commodities) are urgently needed to address the large energy footprint, cost and/or risk associated with existing technologies (e.g. chemisorbents). In particular, water and chemical commodity purification are global challenges, each consuming > 10% of global energy output. SYNSORB will reduce the energy footprint of purification processes through crystal engineering (design), characterisation (structure/function) and modelling (binding interactions) studies that enable understanding of how pore size /chemistry impact the properties and performance of physisorbents. Our objective is to find the energetic sweet spots that enable new benchmarks for selectivity and working capacity for gas (e.g. CH4, C2, C3) and vapour (e.g. H2O) purification at practically relevant conditions. Key scientific impacts include the following: (i) Understanding how pore size/chemistry impact selectivity, binding energy and kinetics of physisorption will afford fundamental knowledge concerning optimal pore size/chemistry for ultra-selective removal of both trace (< 1%) and bulk impurities. (ii) Trace gas removal from even binary gas mixtures was unattainable by physisorbents until recently, when new classes of ultramicroporous materials, HUMs (introduced by the PI in Nature, 2013, and Science, 2016) and AUMs were introduced. The nature of HUMs/AUMs means that they offer new benchmarks for selectivity by > one order of magnitude vs. zeolites and MOFs, thereby enabling removal of trace impurities. (iii) SYNSORB will address purification of multi-component gas mixtures that mimic real world gas mixtures by using bespoke sorbents for each trace impurity (see Scheme below), enabling 1-step removal of multiple impurities for the first time.

PE-19. Degradable Polyolefin Materials Enabled by Catalytic Methods

Plastics are essential to virtually any modern technology and therefore ubiquitious. However, when released to the environment they can persist for centuries. One pillar of a responsible future economy is therefore to endow important plastics with a non-persistent nature. Polyethylene (PE) is the largest scale synthetic material, used in transportation, energy storage, water cleaning, clothing and many other fields. However, it is most problematic concerning

degradability. This proposal addresses this major challenge by introducing photo- and hydrolytically degradable groups in the PE chain. Directly during catalytic PE synthesis, isolated keto groups will be generated by incorporation of small amounts of carbon monoxide. This yet unachieved goal is targeted via catalysts with extreme shielding and rigid ligand environments in heterobimetallic Ni(II) / main group metal complexes. A compartmentalized aqueous polymerization with precise control of high ethylene/CO ratios will yield the in-chain functionalized PE as nano- and microscale particle dispersions. Living catalytic polymerization in nanoparticles is pursued to achieve ultra high molecular weights and gradient PE chains forming nanodomains varying in ketone density. Aqueous heterophase oxidation with benign oxidants on all these nanoparticle will yield in-chain ester groups. Further types of hydrolytically cleavable groups are targeted via the complementary synthetic approach of step growth from seed- or microalgae-oil derived PE-telechelics. This yields linear PE with in-chain carbonate, acetal and anhydride groups. Basic materials properties of all polymers are determined by tensile tests. Degradation studies reflecting a marine environment will indicate the persistency behaviour and fate of microfragments, using macroscopic specimens and the above particles as models. Knowledge of the particle and bulk morphologies will be instrumental to understand the materials and degradation properties.

PE-20. Electronic Neuropharmacology

As the population ages, neurodegenerative diseases (ND) will have a devastating impact on individuals and society. Despite enormous research efforts there is still no cure for these diseases, only care! The origin of ND is hugely complex, spanning from the molecular level to systemic processes, causing malfunctioning of signalling in the central nervous system (CNS). This signalling includes the coupled processing of biochemical and electrical signals, however current approaches for symptomatic- and disease modifying treatments are all based on biochemical approaches, alone. Organic bioelectronics has arisen as a promising technology providing signal translation, as sensors and modulators, across the biology-technology interface; especially, it has proven unique in neuronal applications. There is great opportunity with organic bioelectronics since it can complement biochemical pharmacology to enable a twinned electric-biochemical therapy for ND and neurological disorders. However, this technology is traditionally manufactured on stand-alone substrates. Even though organic bioelectronics has been manufactured on flexible and soft carriers in the past, current technology consume space and volume, that when applied to CNS, rule out close proximity and amalgamation between the bioelectronics technology and CNS components – features that are

needed in order to reach high therapeutic efficacy. e-NeuroPharma includes development of innovative organic bioelectronics, that can be in-vivo-manufactured within the brain. The overall aim is to evaluate and develop electrodes, delivery devices and sensors that enable a twinned biochemical-electric therapy approach to combat ND and other neurological disorders. e-NeuroPharma will focus on the development of materials that can cross the blood-brain-barrier, that self-organize and -polymerize along CNS components, and that record and regulate relevant electrical, electrochemical and physical parameters relevant to ND and disorders

PE-21. Engineering Carbon Nanodots for (Nano)Technological and Biomedical Applications

e-DOTS takes advantage of nanoscale and process-intensification principles, information technology and automation/robotics to translate molecular properties to nanoparticles for use in technologically advanced challenges, ranging from high-quality bioimaging to green catalysis in water. A stringent molecular control over the synthesis and multivalent properties of “carbon nanodots”, 2-5 nm spherical nanoparticles, will allow us to shape a nanofabrication space with engineered functions. The core-shell structure of carbon nanodots, consisting of a confined core and an outer functional shell can be rationally designed by controlled chemical approaches and by a tailored choice of the proper starting materials. e-DOTS scientific objectives are planned to go beyond the state of the art, with the aim to: (i) elucidate the mechanism and the structural details in the conversion of small molecules to nanoparticles; (ii) expand the carbon nanodots preparation process window and allow its automated exploration, directed at ambitious targets; (iii) design and prepare carbon nanodots with tailored properties – in terms of size, charge, luminescence, chirality, and outer-shell functions – outperforming current technologies in green catalysis and biomedical imaging. (iv) investigate and ensure the safety profile of carbon nanodots in a safe-by-design approach. e-DOTS is a highly interdisciplinary project, based on frontier methods that the Prato group has successfully designed for the molecular modification of very diverse carbon nanostructures. Delving into fundamental aspects of carbon nanodots will allow to unfold their full potential in technological and biological applications. e-DOTS will thus offer unprecedented opportunities to the scientific community, since the specific molecular properties of the reactants can be transferred, combined and enhanced up to the nanoscale, yielding carbon nanodots tailored to function.

PE-22. Engineering epithelial shape and mechanics: from synthetic morphogenesis to biohybrid devices

All surfaces of our body, both internal and external, are covered by thin cellular layers called epithelia. Epithelia are responsible for fundamental physiological functions such as morphogenesis, compartmentalization, filtration, transport, environmental sensing and protection against pathogens. These functions are determined by the three-dimensional (3D) shape and mechanics of epithelia. However, how mechanical processes such as deformation, growth, remodeling and flow combine to enable functional 3D structures is largely unknown. Here we propose technological and conceptual advances to unveil the engineering principles that govern epithelial shape and mechanics in 3D, and to apply these principles towards the design of a new generation of biohybrid devices. By combining micropatterning, microfluidics, optogenetics and mechanical engineering we will implement an experimental platform to (1) sculpt epithelia of controlled geometry, (2) map the stress and strain tensors and luminal pressure, and (3) control these variables from the subcellular to the tissue levels. We will use this technology to engineer the elementary building blocks of epithelial morphogenesis and to reverse-engineer the shape and mechanics of intestinal organoids. We will then apply these engineering principles to build biohybrid devices based on micropatterned 3D epithelia actuated through optogenetic and mechanical control. We expect this project to enable, for the first time, full experimental access to the 3D mechanics of epithelial tissues, and to unveil the mechanical principles by which these tissues adopt and sustain their shape. Finally, our project will set the stage for a new generation of biohybrid optomechanical devices. By harnessing the capability of 3D epithelia to sense and respond to chemical and mechanical stimuli, to self-power and self-repair, and to secrete, filter, digest and transport molecules, these devices will hold unique potential to power functions in soft robots.

PE-23. Efficient and Robust Oxide Switching

We are at the beginning of a Data Age. Data is exploding. In 2016, 90% of the world's data ever created was in the two previous years. AI and data analytics are further increasing the growth. The power demand is huge and growing. Within a few years some developed countries will not have sufficient power to sustain the growth. The negative effects on the planet are serious. Non-volatile memory (NVM) technology (including memory and neuromorphic computing elements in a single device) could strongly help to solve the problem, giving two orders of magnitude power reduction and, by removing the data transfer bottleneck, increased speed. Oxide memristors have significant advantages over competing NVM technologies, particularly in terms of speed, cost and temperature stability. However, after more than a decade of intense effort, serious challenges remain in terms of scaling, uniformity and robustness. The

challenges all relate to a lack of precise control of the materials. Completely new thinking in thin film materials engineering is needed. EROS provides this new thinking by designing and engineering new forms of nanostructured oxide films to give highly Efficient, Robust Oxide Switching in an ultra-dense, ultra-low power, reliable oxide memristor system, with potential to change the technology landscape in AI, IoT, and security. 'Ideal' films will first be designed, fabricated, and understood. These will direct the way to simple industry-platform devices. Stochastic effects will be eliminated by creating films with separate vertical nanoscale ionic and electron channels with highly controlled vacancy and electronic concentrations, allowing scaling to a few nm, in a forming-free system. Also, multifunctional hybrid structures will be developed to give robustness. Furthermore, ferroelectricity will be induced, allowing simpler and smaller devices. Confidence in the proposed approach comes from proof-of-concept model systems shown by the PI.

PE-24. Impulsive Flows - beyond velocity and acceleration

My goal is to investigate impulsive flows that occur both in nature and technological applications, where fluid is accelerated due to sudden motion of an object or boundary, which leads to an additional instationary drag or lift forces. This project will shed new light on the understanding of the fundamental properties and flow physics of these impulsive flows. Theoretical concepts that are used today, do not go much beyond those laid down almost 100 years ago. With today's level of technology and experimental tools I will be able to break new ground in the understanding of these flow phenomena that are very challenging both experimentally and numerically. First, a novel-concept flow facility will be built, based on a high performance robotic arm; this robot arm can move and rotate various objects in a water-filled tank along prescribed trajectories with known acceleration and rotation. The fluid motion is measured using tomographic particle image velocimetry (PIV), of which the measurement volume can move along with the objects using auxiliary robot arms. New PIV approaches will be developed that measure fluid acceleration varied within the short times of these impulsive motions. Then a systematic investigation is performed on various impulsive flows where the rate of acceleration and rotation rate can be varied, in order to find new and improved relationships between the measured hydrodynamic force histories and relevant flow quantities, such as velocity, acceleration, and rotation rate, and the time scales at which these phenomena occur. These will represent real-life impulsive flows. Experimental approaches and results will be used to validate numerical methods. The results of this investigation will fill gaps in our knowledge of impulsive flows, and give more accurate estimates of hydrodynamic forces. This

will improve the prediction of structural loads and reduce failure and discomfort, with impact on aeronautics, wind energy, maritime and offshore technology.

PE-25. Towards a full multi-scale understanding of zero-carbon metal fuel combustion

Energy-on-demand is a cornerstone of modern society. Currently, the primary source of energy is fossil fuel, but in view of undeniable climate warming, an alternative fuel is dearly wanted. Metal powders are a tantalizing, totally carbon-free and recyclable option for such a fuel. Its combustion products are solid metal-oxide particles, which, after capture, can be recycled to metal powders again using green electricity. The technology required to burn metal powder aerosols in a stable and reliable way is, however, still in its infancy. Rapid growth of the technology is unlikely, because fundamental understanding of combustion of dense metal aerosols is largely lacking. Herein lies a virgin field of fundamental research, with huge potential for practical application. Fundamental principles behind metal fuel flames are addressed in this proposal, in a step-wise, combined experimental & theoretical/numerical approach. On single-particle level, I will unravel the influence of mutual interactions. Their consecutive ignition will create combustion wave fronts traveling through metal aerosols. Such planar flame fronts will be created in the lab as well as studied numerically and subsequently used as building block for modeling 3D flames. Finally, Bunsen-type burners will be developed to characterize turbulent, 3D flames. Detailed experiments using microscopy for metal-(oxide) particle composition as well as new optical diagnostic techniques on dedicated, lab-scale metal aerosol burners will serve as benchmarks for validation of models. I have a 30 years track record in theoretical, numerical & experimental combustion research, focusing on fundamental aspects of combustion processes relevant to practical applications. In this project this experience will be the foundation from which to explore a new direction in fundamental combustion research. This METALFUEL project will boost to a new branch of combustion research, with the potential for disruptive applications.

PE-26. Multiscale modeling and simulation approaches for biomedical ultrasonic applications

Ultrasound-guided drug and gene delivery (USDG) enables controlled and spatially precise delivery of drugs and macromolecules, encapsulated in microbubbles (MBs) and submicron gas vesicles (GVs), to target areas such as cancer tumors. It is a non-invasive, high precision, low toxicity process with drastically reduced drug dosage. These advantages open doors to numerous biomedical applications, from sonothrombolysis to blood–brain barrier opening.

However, the progress and deployment of this technology is subject to extensive experimentation and heuristics. The proposal aims to develop a virtual environment to quantify and optimize USDG and in particular the MBs and GVs utilized as drug carriers and contrast agents. Their type and concentration, and interface with ultrasound (US) are critical to the success and efficiency of USDG. State-of-the-art USDG systems operate in a narrow range of empirically-tuned US parameters. This empiricism entails severe risks and limitations for clinical applications and delays the adoption of this potent technology. I propose a computational framework that would allow for controlled testing, data-driven quantification of uncertainties, and a rational optimization of experimental US parameters. The framework will rely on submicron resolution modeling and simulation of cavitating MBs and GVs interacting with US. Limitations of existing models based on continuum theory preclude an accurate description of cavitation, drastically degrading the prediction of drug delivery outcomes. I will develop new, data-informed mesoscopic models of US contrast agents, capturing their rheological and acoustic behavior. Specific interactions of US and agents at a submicron level will be included by harnessing novel multiscale methods that enable seamless propagation of US from the macro to microscopic level. The proposed framework will be integrated with experimental efforts to advance USDG across biomedical applications.

PE-27. Nature-inspired Circular Recycling for Polymers

In 2070, 10^12 Kg of plastics (polymers) could be produced yearly in a world inhabited by 11 billion people. Hence, we have ~50 years to address this sustainability challenge. The sourcing and disposing of such quantities without a significant environmental impact will not be possible, even if everything is bio-sourced and bio-degraded. Yet, on earth, there are >10^12 Kg of proteins (one of Nature's polymers). They are sustainable because they are recycled in a circular way. If we exemplify their metabolism, proteins are decomposed by living organisms into their monomeric constituents (the amino acids, AAs); the cell machinery uses such AAs to synthesize new proteins that have little in common with the original ones. This is only possible because a protein is a specific sequence of AAs bound together by cleavable peptide bonds, i.e. proteins are sequence-defined polymers, SDPs. Nature reuses and does not degrade AAs, thus assuring protein sustainability. This project aims at showing that such a circular approach to recycle SDPs is possible for technologically-relevant polymers using engineering-sound laboratory processes. One aim is to show that b-Lactoglobulin, a milk protein used as a component for water filtration membranes, can be digested into its AAs, that, in turn, can be used to form Fibroin, a silk protein used in resistive switching memory devices. Fibroin will be converted

into Keratin, a wool protein, that will be converted back into b-Lactoglobulin. Another aim is to perform the whole process within an automated and scalable robotic platform. The final aim is to expand this concept from natural proteins to DNA and non-natural SDPs. There would be a paradigm shift in plastic recycling, if a random mixture of any polymers could be used to produce any other polymer on earth, without taxing the planet with degradation products. Scope of this project is to show that such a vision in the circular use of polymers is scientifically and technologically possible.

PE-28. The Physics of Metal Plasticity

The societal need to conserve materials and energy calls for lighter and stronger metal components. The advantage of metals is their unique combination of plasticity (i.e. formability) and strength, which is governed by their complex structure. This structure is organized hierarchically on several length scales. In contrast to functional materials and polymers, this complexity has led to the common theoretical framework being not physics, but an engineering science: metallurgy. As a result, phenomenological models prevail. The big obstacle to understand the underlying physics is the lack of visualization of the dynamics of the structure. From 2012 to 2019 I have developed a hard x-ray microscope for high-resolution 3D studies. Uniquely, this now allows us to zoom into the material and map grains and dislocations. This will enable 3D movies on all relevant length scales. No competing group will have anything similar within the next 5 years. PMP will exploit this to unravel the physics of plasticity. For the first time, we can directly see the processes involved: the creation of dislocations, their self-organization, and subsequent creation of ever more complex patterns. At the same time, we can deduce the local stress. This will provide answers to longstanding core questions of metal science. Current multiscale models of plasticity are not capable of predicting realistic patterns. The new data will guide theory and allow for direct comparison of models and experiment at all scales. PMP will develop a physics-based multiscale model of plasticity that for the first time can predict which patterns evolve when and where in the metal, and as a result greatly improve predictions of the macroscopic plasticity and strength. If successful, we have created the instrumental and modelling foundation for a new paradigm in structural materials. This will support the ultimate vision of materials and process design in computer models rather than trial and error in the lab.

PE-29. Full human-based multi-scale constructs with jammed regenerative pockets for bone engineering

Engineered bone tissue has been viewed as a potential alternative to the traditional use of bone grafts, due to their limitless supply and no disease transmission. However, bone tissue engineering practices have not proceeded to clinical practice as it was not yet possible to fully recreate the right conditions to produce relevant large vascularized grafts and enabling their in vivo integration and remodelling. REBORN proposes rather unique toolboxes combining bionstructive biomaterials only based on human proteins obtained from the amniotic membrane (AM) and cells from the umbilical/blood cord for the ground-breaking advances of engineering totally time-self-regulated complex 3D devices, able to adjust the cascade of processes leading to faster high-quality and vascularized new bone tissue formation with minimum pre-processing of cells. Proteins from AM will be chemically modified with bioorthogonal clickable moieties enabling their selective association during the fabrication of liquified pockets or hydrogels. Perm-selective AM-protein membranes will be formed at the interface of aqueous-based emulsions to produce liquified pockets confining all necessary ingredients for internal in vitro tissue development to recreate the bone niche including: (i) the correct cells' ratio, (ii) hydrogel MicroBlocks that will provide geometrical, mechanical and topographic cues to control cellular behaviour and (iii) bioactive soluble factors. Jammed liquified pockets will be assembled into a final desired implantable device, bound by the developed hydrogels, with clinically relevant size, shape and structural integrity, using non-conventional 3D bioprinting processing methodologies or by physical fixation in bioinspired, periosteum-like, regenerative membranes. Advanced techniques will be employed to characterise the new tissue developed in the hybrid devices, from the ultrastructure of the mineral/organic component, including under distinctive dynamic culturing conditions.

PE-30. Rheology of yield stress fluids: a multiscale approach

Yield stress fluids defy our conventional notions of liquid and solid, keeping their shape as soft solids at low loads, yet yielding and flowing like liquids at larger loads. They can then suffer arbitrarily large deformations in this liquid state, but will recover a solid state if the load is removed. Their internal microstructure and macroscopic shape are thus determined directly by the processing history they experience. Such materials are all around us: in colloids, microgels, emulsions, foams, pastes, slurries, and their biological counterparts. They find widespread applications in foods, pharmaceuticals, construction, oil extraction, lubricants, coatings, etc.

Despite this importance to so many engineering processes, we still do not understand how their remarkable macroscopic rheological (deformation and flow) properties emerge out of the collective dynamics of their constituent microscopic substructures: colloid particles, microgel beads, emulsion droplets, etc. Addressing key questions emerging from recent experiments, RheoYield aims to build new theories to inform and potentially transform our understanding of the rheology of yield stress fluids. Within a multiscale approach, the project will capitalise on rapid recent progress in understanding how microscopic rearrangement events cooperate to give macroscopic flow. Using theoretical and computational tools that I have recently developed, and new ones that will be developed here, RheoYield aims to: 1. Identify the microscopic changes that take place in a soft solid as it slowly yields into a fluidised state. 2. Understand the profound influence of boundary physics on bulk yielding. 3. Develop the first microscopically founded continuum constitutive model that captures all the key features of yield stress rheology. 4. Establish a microscopically founded computational fluid dynamics of yield stress fluids. 5. Develop basic new science underpinning strategies for the optimised control of yield stress rheology.