ERA-NET NEURON Cofund2

Foresight symposium

"Blood-Brain Barrier and Cerebrovascular Diseases"

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Virtual meeting

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Inserm, France

This Foresight symposium is part of the Work Package

"Outreach and interaction activities"

Work Package leaders are Inserm and CNRS

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Welcome

Dr. Marlies Dorlöchter, DLR-PT - NEURON coordinator (Germany)

Marlies Dorlöchter, as coordinator of ERA-NET NEURON, introduced this foresight symposium on 'Neurodevelopmental disorders' by welcome addressing all attendants: scientific speakers, representatives of patient organizations, members of the NEURON Scientific Advisory Board, and representatives of NEURON partner organizations. She highlighted the value of this meeting for funding organizations to identify the important questions that should be addressed in a future call-for-proposal.

ERA-NET are networks of funding agencies and ministries, in Europe and beyond, getting support from the European Commission. NEURON (Network of European funding for Neuroscience research) is an ERA-NET in the area of brain research. Starting in 2003 with four funding organization it developed constantly and comprises today 26 funding organizations with partners well beyond Europe such as Canada and Taiwan. One of the key elements of NEURON is launching Joint Transnational Calls (JTCs) for research proposals, because multilateral, interdisciplinary innovative research is key to explore the brain and its diseases, and to help finding therapies and diagnosis tools for various disorders. A special feature of NEURON are the calls for proposals for research projects on Ethical, Legal, and Social Aspects (ELSA) of Neuroscience, a unique international funding instrument. NEURON's purpose as a network is not only to promote brain research, but also to improve interactions between the research community, policy makers, funding organizations and the general public. In discussions with European and national policy makers NEURON strives to gain enhanced consideration for brain research. It also interacts with the research community in various formats such as foresight symposia, workshops, newsletters and journal editorials. NEURON also includes programs to support early-carrier researchers such as inviting them to networking activities and FENS conferences as well as the Excellent Paper in Neuroscience Award.

The topic of "Blood-Brain Barrier and Cerebrovascular diseases" was obtained from the merging of two subjects highlighted in the 2020 update of the NEURON Strategic Research Agenda (SRA). One of the new topics highlighted in this update is the importance of conducting research not only on neuronal networks but also on non-neuronal cells and their interactions with neurons. Indeed, impairments on the non-neuronal compartments have been linked with neuronal dysfunction and the development of neurological diseases. Recent advances have allowed for new approaches for studying these mechanisms, urging toward more multidisciplinarity in brain research. In addition, the SRA highlighted how cerebrovascular diseases are among the most life-threatening neurological events and are at high risk to cause severe long-term disabilities.

These activities are based on a research strategy: world experts from various scientific fields and from the NEURON Scientific Advisory Board developed a Scientific Research Agenda (SRA). It was first published in 2016 and recently updated in 2020. The SRA covers the entire field of brain diseases: brain research on neurological diseases, psychiatric disorders, sensory organs diseases and peripheral nervous system disorders. The priorities covered in NEURON calls and other activities are to understand diseases mechanisms, to understand disease progression, and develop interventions. In the process of publishing SRA, the research communities (namely professional societies and patient organizations) were also asked for their input on this research agenda, and NEURON can comfortably rely on 80% approval or even entire acceptance.

Introduction

Dr. Etienne Hirsch, INSERM (France)
Dr. Bernard Poulain, CNRS (France)

Cerebrovascular diseases cause a major burden on health worldly, with stroke being the second leading cause of death and a major cause of disability (Katan and Luft, 2018). Yet there are many mechanisms involved in cerebrovascular diseases, with conditions than can develop years before the clinical features are observed in patients, and it is important to understand the different aspects of these conditions. This is a very broad area, going from basic research on the function of the blood-brain barrier to rehabilitation strategies after cerebrovascular incidents.
NEURON funding organizations thus agreed on the importance for the neuroscience research community to work towards uncovering the mechanisms of cerebrovascular diseases and to investigate novel therapeutic concepts. This symposium served as a consultation step for the NEURON funding organizations to receive a scientific update on the topic, and we are grateful to the experts whose insights help us in developing valuable activities for brain research

This symposium has several general objectives:

- To provide an overview of the major NDDs
- To review normal development of the nervous system
- To review the genetic background of NDDs
- To present a focus on ASD and childhood epilepsy syndromes
- To address the burden of NDDs and intervention strategies
- To discuss about a possible call focused on NDD research

To cover these aspects, experts have been invited to highlight hot topics and challenges, and representatives from patient organizations will complete these advices with the patient view, in order to prepare the next joint transnational call on cerebrovascular diseases.

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General overview on the brain-blood interface

Dr. Steven Proulx and Prof. Britta Engelhardt (not attending)
Theodor Kocher Institute, University of Bern, Switzerland

The separation of the brain parenchyma from other compartments, including blood, is ensured by several barriers surrounding the central nervous system (CNS). The most well-known of these is the blood-brain barrier (BBB) which allows for fine regulation of the exchange of molecules and proteins between the CNS and the systemic circulation. Contrary to what is observed in the normal peripheral vasculature, the BBB shows little to no pinocytotic vesicles, but complex tight junctions so that entry and exit of molecules relies instead on adsorptive or receptor-mediated transcytosis.
In addition to the BBB, other barriers isolate the brain and define the subarachnoid space containing cerebrospinal fluid (CSF). The surface of the brain is protected by the pia mater, while the subpial space comprised between pia mater and glia limitans also contains some blood vessels. CSF also has access to the perivascular space, a separation between vascular wall and the glia limitans (where the parenchymal basement membrane and astrocyte end-feet form the final separation with neurons and parenchyma cells). This space contains several types of cells, including smooth muscle cells, fibroblasts and a resident population of macrophages. At the borders of the CNS, the arachnoid barrier forms an important separation between the subarachnoid space and the dura mater, a tissue containing permeable blood vessels, thus is outside of the CNS compartment itself. Lastly, another barrier lies at the choroid plexus, within the brain ventricles: a thin layer of tight-junction epithelial cells known as the brain-CSF barrier that separates the fenestrated microvessels within the stroma of the choroid plexus from the ventricular space.
These barriers are highly selective in the cells and molecules they allow in and out of the brain parenchyma, and thus play an important role in both the normal function and the protection of the central nervous system. They allow for maintenance of fluid and ion homeostasis, necessary for proper neuronal function, and provide fine regulation of the waste removal from the brain compartment. At the same time, these barriers are known for their protective role, by limiting the exposure of the CNS to antigens and toxins, and by establishing an immune privilege within the CNS parenchyma.

Central nervous system as an immune privileged organ

Work on allografts performed by Sir Peter Medawar back in the 1940s, as well as the lack of constitutive expression of MHC class I and II proteins on parenchymal cells and the lack of lymphatic vessels within the CNS all suggest that the brain parenchyma is an immune privileged site: there appears to be no direct immune surveillance of the brain parenchyma, in contrast to the CSF compartments. Brain barriers play an important role in ensuring this immune privilege, protecting the central nervous system from inflammatory responses, and building understanding of their mechanisms is instrumental in this regard. Still, immune cells can cross these barriers, and work on disease models has played a major role in unveiling the mechanisms of a multi-step recruitment of immune cells across brain barriers during CNS immune surveillance and neuroinflammation.
Studies on EAE mice (a model for multiple sclerosis), for example, allowed for investigation of how autoaggressive CD4+ T cells cross the BBB at the postcapillary venules, despite not being a very permissive site: the endothelial cell barrier of these venules is defined by very tight junctions ensured by molecules such as claudins and occludin. Observations with two-photon in vivo microscopy has highlighted how the T cells crawl for extended distances against the direction of blood flow along the luminal side of the BBB in search for a permissive site like BBB tricellular junctions for diapedesis. After

crossing the endothelial cell layer the immune cells reach the perivascular space. Work employing live cell imaging and in vitro microfluidic assays on brain endothelial cells allowed for characterization of the different mechanisms involved in multi-step T cell extravasation across the BBB. In normal conditions, T cells can cross the barrier preferably by diapedesis through tricellular junctions, where three endothelial cells are meeting (although diapedesis through bicellular junctions also occurs). In addition, T cells can also cross an inflamed barrier (in vitro, by addition of IL1-beta) by transcellular diapedesis, exiting through a pore through the endothelial cells themselves toward the perivascular space. Similarly, other immune cells can reach the perivascular space: for neutrophils for example, the situation in the CNS is different from peripheral organs, where pathogens-associated and damage-associated molecular patterns (PAMPs and DAMPs) are known inducers of their recruitment. It is the presence of inflammatory cytokines or chemokines in the brain that lead to recruitment of neutrophils, the immune cells reaching the perivascular space, CSF space or subpial space. Similar observations are made with monocyte/macrophages: no immune cells are able to breach the glia limitans into the brain parenchyma in normal conditions.

In EAE models on the other hand, immune cells seem to find their way from perivascular spaces into the parenchyma, and that is the starting point for the appearance of clinical features. Recent work suggests that immune cells cross the glia limitans through the action of factors such as matrix metalloproteases (MMP-9 and MMP-2) produced by astrocytes and macrophages accumulating in the perivascular space. These metalloproteases degrade extracellular matrix receptors of astrocytes, allowing the immune cells from the perivascular compartment to exit into the brain parenchyma.

Additionally, other sites have been identified as potential routes for the entry of immune cells into the CNS, which remain to be further identified. Chemokine-signalling (CCL20 and CCR6) allows the T cells to enter the choroid plexus, yet it is unknown how they can migrate through the epithelial cell layers toward the CSF. In vivo imaging studies of the meninges of the spinal cord have also provided evidence of immune cells exiting here from the blood vasculature in rodents.

Drainage of the central nervous system

The historical concept for drainage of the CNS suggests that CSF from the subarachnoid space finds its way through the arachnoid villi to the dural venous sinuses, by a mechanism that has never been elucidated. On the other hand, tracer studies in various mammalian species have shown transport to the lymphatic vessels located near the exit points of cranial or spinal nerves after injection into the CSF, suggesting a similar role of the lymphatic system for the CNS as for peripheral tissues. In the last 7 years, the meningeal lymphatics in the dura mater have also been implicated in CSF clearance. At this time, through any of these potential efflux routes, it is still unclear how CSF crosses the arachnoid barrier to reach the lymphatic system.

Studies have shown intravascular tracer leaks into the dura, without leakage through the other CNS barriers to the pia and brain parenchyma, suggesting that the dura mater does not have the same permeability as other barriers since it is localized outside of the CNS. Recent studies involving tracers injected into the CSF of mice have identified CNS outflow routes localized around the exit of cranial nerves: through the cribriform plate near the olfactory bulb (where the olfactory nerves emerge), at the exit of trigeminal nerves, as well to lymphatics exiting near the orbit of the eye (suggesting a route along the optic nerves) and at the base of the skull near the jugular foramen.

Finally, MRI observations using low-rate infusion of tracer into the lateral ventricles in mice seem to confirm two main CSF efflux routes: first along the cranial nerves and at the base of the skull (e.g. jugular foramen), toward mandibular and deep cervical lymph nodes, and secondly along the spinal

cord to drain from the spine sacral end to the iliac and sacral lymph nodes. Still, further clarification is needed on these outflow routes, including their potential role in immune responses of the CNS.

In addition, the glymphatic concept, a model first described in 2012, suggests that CSF flow in the perivascular space around cerebral arteries, up until the capillary level where this paraarterial influx finds a route into the brain parenchyma across the astrocyte vascular endfeet (either through aquaporin AQP4 channels or gaps between the endfeet). According to this model, a convective glial-mediated flow goes through the brain parenchyma, taking up metabolites and interstitial fluids, to exit through unelucidated perivascular routes along the veins, eventually reaching to the lymphatic system. This concept is very controversial from an immune surveillance standpoint, as a steady flow through the brain would allow antigens to reach the CSF quickly, which differs from the delay in the immune response observed from allograft studies. Indeed, tracer studies in mice, in living conditions, showed a flow from the lateral ventricles to spaces surrounding both arteries and veins on the brain surface, but not the suggested flow into the brain tissue itself. Only at the time of death of the mouse is the periarterial influx observed, as has also now also been observed after ischemic stroke.

In conclusion, there is still much to be elucidated regarding the effects of the brain barriers on fluid homeostasis in the CNS and how these barriers help to orchestrate CNS immunity.

General overview on small-vessels diseases

Prof. Élisabeth Tournier-Lasserve
Lariboisière Hospital, University of Paris, France

Cerebral small vessel diseases (CSVD) are “neuroimaging & neuropathological abnormalities in the cerebral white and deep grey matter thought to arise from abnormalities of perforating cerebral arterioles, capillary & venules » (Wardlaw et al, 2019). CSVD account for 25% of stroke and 45% of dementia, and also cause walking disabilities and other handicaps. Their prevalence increases importantly with age, from about 5% at 50 years old to almost 100% (yet not always symptomatic) above 90 years old. CSVD neuroimaging shows an association of white matter hypersignals, which are not specific to CSVD but show peculiar distribution in these diseases, and microvascular lesions, including deep small infarcts, hematoma or microbleeds.

There is very limited knowledge on the pathogenic mechanisms of CSVD, hence no specific treatment except for the control of well-established risk factors such as hypertension. This is partly due to the strong heterogeneity of these disorders, with several classes being identified so far: arteriosclerosis (the most frequent one), cerebral amyloid angiopathy, inherited monogenic CSVD, inflammatory-mediated or immunologically-mediated CSVD, and others (Pantoni, 2010).

In comparison with sporadic “common” CSVD associated with arteriolosclerosis, inherited monogenic CSVD are much rarer yet they can share similar neuropathological features. Monogenic CSVD have thus been instrumental in unravelling the mechanisms of these disorders. However, these monogenic CSVD are highly heterogeneous in terms of inheritance patterns, genes and mechanisms. They can affect either small intracranial vessels or both small and large vessels. Some of them include extraneurological clinical manifestations, and while age is a major factor for sporadic CSVD, some monogenic CSVD can even affect foetuses and children. In the last 30 years, several monogenic disorders have been identified, leading to the development of diagnostic tools and cellular and animal models relevant to study both monogenic and “common” CSVD.

In this overview, we will first summarize the lessons drawn from 2 emblematic monogenic CSVD and then point out the next challenges to overcome in this field.

CADASIL and NOTCH3-related CSVD

Identified in 1996, CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts & Leukoencephalopathy) is an autosomal dominant disease with a very high penetrance (for a recent review, see Chabriat et al, 2020). “Classical” CADASIL is a severe disease starting around 45 to 50 years old with a long asymptomatic period, leading to migraine with aura, recurrent lacunar infarcts, mood disorders, apathy, cognitive impairment, dementia and an early death (around 65 years old). MRI shows leukoaraiosis, deep lacunar infarcts, microbleeds, enlarged perivascular spaces, and cerebral atrophy. Electronic microscopy allows to observe the accumulation of granular osmiophilic material in the basal lamina of vascular smooth muscle cells and pericytes in brain vessels, a specific neuropathological marker that had been instrumental in the earlier investigations of this disease.

The gene responsible for CADASIL encodes the Notch3 transmembrane receptor. CADASIL-type variants are highly stereotyped, leading to an odd number of cysteine residues in the extracellular EGF-like repeated motifs of Notch3. Thanks to mechanistic studies conducted on tissues and animal models in the past 25 years, we now have a better understanding of this disease: the aggregation of mutated Notch3 protein has been identified as the starting point of pathological events leading to the abnormal recruitment and dysregulation of various extracellular matrix proteins. This growing understanding of

the disease mechanisms allowed the development of preclinical cellular and animal models used to investigate potential therapeutic strategies such as mutation exon skipping or immunotherapy using antibodies directed against Notch3.
CADASIL accounts for 10 % of familial CSVD cases, with a prevalence estimated until recently to 2 to 4 out of 100.000 in the general population. However, recent genotype data from several databases, including ExAC and UK biobank, suggest that one person out of 500 in the general population carries a CADASIL-type Notch3 variant (Rutten et al, 2020; Cho et al, 2020). Interestingly, the location of these CADASIL-type variants differs when comparing cohorts of patients referred for NOTCH3 screening in a diagnostic context and population based databases. Altogether, these data strongly suggest that some of these CADASIL-type variants may be risk factors for non monogenic stroke and vascular dementia, and raise important questions as regard to mechanisms and modifying genes. Solving these questions and developing efficient therapeutic approaches for CADASIL are some of the main challenges to overcome in this field.

COL4A1 angiopathies

With their extreme phenotypic and molecular variability, COL4A1/COL4A angiopathies are a striking example of how heterogeneous monogenic CSVD are.
Identified in mice first and later on in human families, glycine missense or loss-of-function COL4A1/COL4A2 mutations are associated with intracerebral haemorrhage and a number of extra-neurological manifestations at any age, from fetal life to adulthood. The two main hypotheses for the starting point of the disease at the cellular level is that mutated proteins are trapped in the endoplasmic reticulum and lead either to an insufficient amount of COL4A1/COL4A2 subunits in the extracellular matrix or to a toxic effect of their accumulation in the reticulum. A recent COL4A1 mouse model study highlighted the role of a hypermuscularization of the transitional segment between arterioles and capillaries which, combined with a loss of vascular smooth muscle cells upstream, is suspected to be responsible for the haemorrhages.
Distinct mutations causing an upreglation of a normal COL4A1 protein were shown to cause a different disease CSVD called PADMAL. This severe CSVD is known to affect only adults, to be fully penetrant, and to cause ischaemic stroke without cerebral haemorrhage nor extraneurological involvement. Yet, the mechanisms leading to ischaemic stroke in PADMAL remains to be unravelled and the lack of animal models for upregulation of COL4A1/A2 is a major challenge for further investigations.

Next challenges for cerebral small-vessel diseases

Although the mechanisms of some CSVD such as CADASIL start to be unravelled, a lot of work remain to be done in the field. The development and multi-modal investigation of relevant animal models for monogenic CSVD is critical. While the causative genes have been identified in at least 12 CSVD we still lack a proper animal model for most of these. It is only by building up knowledge on the mechanisms, for both familial and sporadic CSVD, that we will allow progresses toward clinical trials. Especially as, despite the progresses on therapeutic strategies, translation of the preclinical data in humans remains a major hurdle for CSVD.
Additionally, strong efforts are necessary to identify missing genes for monogenic CSVD, which proved to be a helpful strategy to understand these diseases. Indeed, as much as 80% of familial CSVD patients referred for molecular screening do not show mutation in known CSVD genes. Developing novel computational and statistical tools will be critical to decipher this highly heterogeneous group of diseases.

Stroke genetics: Discovery, biology, and clinical implications

Prof. Martin Dichgans
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The field of stroke genetics has kept bringing new achievements, allowing for major changes of how we understand stroke. Cerebral small vessel disease is a good example: what has previously been considered a single disorder is now recognized to be a heterogeneous condition with multiple genetically defined disorders. Genetics provides unique opportunities to dive into the mechanisms of cerebrovascular diseases, leading to new ways to classify and study them. For instance, genetics has pointed to the role of an altered extracellular matrix with specific molecules, such as collagen Col4A1 and Col4A2 (involved in CARASAL), cathepsin 1 (involved in HANAC), Notch3 (involved in CADASIL), and HTRA1 (involved in CARASIL) moving into focus. This refined classification of cerebrovascular disease is important for unravelling the underlying mechanisms, but it can also be turned into a framework to investigate targeted treatment approaches.

As an example, CARASIL is a rare disease first identified in families with recessive small vessel diseases and early age of onset, leading to dementia and stroke as well as other symptoms such as hair loss. It is caused by rare loss-of-function mutations of the high temperature requirement protease HTRA1, a serine protease that is secreted into the extracellular matrix were it cleaves latent beta-binding protein LBTP-1, which in turn is involved in the TGF-beta signalling pathway. While homozygous mutations cause CARASIL, carriers of heterozygous mutations of HTRA1 exhibit an autosomal dominant form of small vessel disease, more similar to the sporadic condition, notably with a later age of onset. In addition, recent work using whole-exome sequencing in participants from the UK biobank found that HTRA1 is among the key molecules involved in ischemic white matter hyperintensities. The mutations identified here appeared to be confined to the protease domain and result in loss-of-function very similar to what is observed in CARASIL. These findings add to the expanding spectrum of these mutations, not only in families with CARASIL but also in the general population, with a mutation frequency of around 1 in 450.
In CADASIL, another monogenic small vessel disease caused by NOTCH3 mutations, investigations highlighted a colocalisation of Notch3 and HTRA1 in brain vessels. Based on this idea, further proteomic studies showed how several proteins are accumulating in brain vessels both in CADASIL brains and in HTRA1 knock-out mice, with most of these proteins being substrates of HTRA1. Thus, proteomic investigations helped unravel the diseases mechanisms and how Notch3 accumulation in CADASIL sequesters not only proteins such as TIMP3 and VTN, but also HTRA1, potentially mediating some of the disease mechanisms.

Common genetic variants as a starting point for discovery

In addition to the aforementioned rare variants associated with Mendelian disorders, more and more common variants are being identified that are implicated in sporadic forms. These gene loci provides additional mechanistic insights (pointing towards topics such as blood-brain barrier, angiogenesis, smooth muscle cell functions and so on), as well as highlighting the potential overlap of genes implicated in the disorders.
Genome-Wide Association Studies (GWAS) have been instrumental in identifying novel genes implicated not only in stroke in general, but more precisely in ischemic, large artery, cardioembolic or small vessels strokes. A number of the genes identified in GWAS are known targets for approved

antithrombotic drugs (such as FGA targeted by alteplase and PDE3A targeted by cilostazol), and building confidence in GWAS would thus allow to build a growing list of loci to drive the development of stroke therapy. A demonstration of this lies in the discovery chain of Histone DeAcetylase 9 (HDAC9), an important locus for large artery arteriosclerotic stroke also associated with coronary and peripheral artery diseases: initial observations allowed moving from expression quantitative trait loci to mechanistic studies, up to drug development in humans. It was shown that HDAC9 binds to and activates IKK-alpha and beta, both key molecules in canonical NF-kB signalling, prompting the pro-inflammatory response with secretion of pro-inflammatory cytokines in macrophages, atherosclerotic lesions and epithelial cells. Pharmacological inhibition of HDAC by TMP195 was thus investigated, showing promising results during in vivo studies in mice on reducing the early lesion size in atherosclerotic diseases, as well as a stabilizing effect on advanced atherosclerotic plaques.

Mendelian Randomization for exploration of drug targets

GWAS can also be leveraged further for Mendelian randomization (MR), which uses genetic variants causally related to an exposure, such as circulating levels of specific cytokines, and tests their association with an outcome, such as stroke. This method allows to conduct “in silico trials” that investigate causal relationship with risk factors or drug responses, based on informative genetic datasets.

As an example, GWAS data on circulating cytokines and growth factors were used in 2019 to genetically predict how elevated levels of circulating monocyte chemoattractant protein MCP1 are associated with increased risk of stroke (even characterizing variation of the risk per ischemic stroke subtypes). These results were further consolidated with observational data collected from prospective cohort studies with measurement of circulating MCP1 levels, and meta-analysis even showed a dose response relationship between MCP1 levels at baseline and risk of subsequent stroke as well as other cardiovascular events. This even prompted more investigation on the underlying mechanisms and the association of MCP1 levels in human atherosclerosis with key factors of plaque vulnerability. These recent studies illustrate the “triangulation of evidences”, where human genetics (through MR), observational data on multiple outcomes and experimental data all provide converging evidences, a situation that is a strong starting point for conducting clinical trials on novel treatments.

Not only has MR proven useful in exploring novel drug targets, it can also be a decisive tool for identifying the best treatments for stroke subtypes. Increased blood pressure, for example, is a known risk factor for stroke, with hundred of associated genetic variants. By testing in MR variants located in known drug targets for hypertension (such as ACE inhibitors, Ca-channel blockers and beta-blockers), it is possible to investigate the effects of these drugs in individual stroke subtypes, which can rarely be looked upon in clinical trials. As an example, a 2020 MR study showed that while Ca-channel blockers are more effective than beta-blockers on reducing stroke risk, they are very effective for small vessel strokes in particular.

With a complementary approach to GWAS, phenome-wide association studies (PheWas), it is also possible to assess side effects of drugs and repurposing opportunities. Looking into biobanks for multiple phenotypes and a single set of variants, it is possible to identify association of these variants with other effects. In a 2019 study, genetics variants in drug targets for Ca-channel blockers were showed to be associated not only hypertension and circulatory diseases, but also diverticulosis, and such side effects were confirmed by observational data. Similarly, MR approaches were expanded to blood lipids, showing a protective role of elevated HDL cholesterol (namely for medium size HDL particles), with high circulating levels associated with lower risk of stroke and lower white matter

hyperintensities volumes. Expanding this to HDL cholesterol lowering genetic proxies for the effects of CETP inhibitors even showed similar results, diving into exploring the effects of individual drug classes. These examples again illustrate how genetics allows for predictions that can be turned into prospective studies.

Genetic risk prediction

With the increasing knowledge on risk factors for vascular diseases, it is becoming clear that not only lifestyle factors (reflected for example by the Framingham score) but also genetic factors should be taken into account to predict the risk of stroke for patients.

Given the amount of genetic risk variants that are being identified, information from GWAS can prove critical to generate genome-wide polygenic scores for specific conditions. This indeed providing a robust tool to identify people with higher genetic risk of stroke, scores that can even be used with other measures, for example combining lifestyle and genetic risk profiles. Interestingly, combining these scores showed that people with high genetic risk but favourable lifestyle have a comparable risk to people with low genetic risk and intermediate lifestyle. It is a critical observation, meaning that it is possible to balance a higher genetic risk, even more with early intervention to prevent the external risks from accumulating.

Still, there are important efforts to foster regarding the development and validation of polygenic risk scores, and many challenges need to be faced for their implementation in the clinic.

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State of the art of preclinical research on stroke

Prof. Anna Maria Planas
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Some of the mechanisms contributing to neuronal cell deaths in ischemic stroke and the progression of damage have been known for a long time. The historical approaches are mostly neuron-centric ones, with researches pushing toward prevention of neuronal death. It has since been demonstrated that such approaches are insufficient, and a new concept arose on providing an integral protection of the brain in case of stroke, preserving not only neurons but also endothelial cells and the complex junctions within the blood-brain barrier.
Indeed, in stroke the blood-brain barrier (BBB) plays an important role in the injury. Investigations with tracers and dyes in animal models highlighted important changes in permeability of the BBB following ischemic stroke, either transient and reversible in the earlier phases or irreversible later after the onset. The dynamic alteration of the BBB is a very complex topic, with many mechanisms that remain unknown, and protecting the BBB presents a major functional challenge in stroke.

Mechanisms involved in vascular dysfunction after ischemic stroke

Many factors can affect the changes in the barrier permeability, such as age, lifestyle triggering vascular dysfunction, predispositions to BBB damages, and genetic background with both rare risk factors and common variability. Over recent years, several molecular determinants responsible for the damage and dysfunction of the BBB in stroke have been identified, such as matrix metalloproteinases, cytokines, chemokines, growth factors, protease activated receptors (such as complement, plasmin, or thrombin), lipid mediators, and others. On the other hand, metabolites such as dimethyl fumarate have been used to reduce the brain oedema and protect the BBB after stroke.
Matrix metalloproteinases (namely MMP-9 and MMP-2) in particular are known for their critical role in BBB breakdown, and as such are an interesting topic for preclinical research. Studies highlighted how they are activated at different timepoints after stroke, with variable levels of activity, while animals deficient in MMP-9 show a lower degree of BBB dysfunction. Yet metalloproteinases are important components of the repair response of the tissue so while they damage the barrier during the acute phase of stroke, they also contribute to its repair in later phases.

The role of oxidative stress in vascular dysfunction in ischemia is another main topic of research and a potential therapeutic target. Large vessel walls and capillaries have been identified as major sources of oxidative stress. Indeed, NADPH oxidases in the endothelial cells can generate superoxide, while other compounds accumulating after stroke generate nitric oxide, resulting in the formation of peroxynitrite. By activating matrix metalloproteinases MMP-9 and MMP-2, generation of such molecules is a cause of disruption of the BBB. Additionally, other mechanisms have been highlighted to be triggered by oxidative stress in the brain vessels, such as contraction of the pericytes, impairing the capillary reflow, or mitochondrial electron leakage providing reactive oxygen species.
Scavengers of peroxynitrite and other reactive oxygen species are thus important targets for treatment to protect the BBB after stroke. Several antioxidant drugs have been investigated in brain ischemia, for instance studies with the natural antioxidant uric acid provided evidences suggesting that it reduces protein nitrotyrosination, which is an irreversible protein modification that impairs protein function and drives vascular dysfunction. Indeed, administration of uric acid in rodents has shown consistent

results in reducing the infarct volume after stroke, as well as exerting many protective effects. Yet a major challenge remains in translating these results into humans: so far, clinical trials showed insufficient outcomes, yet promising trends for patients with high blood glucose (due to their higher risk of oxidative stress), and larger trials are needed to demonstrate efficacy.
Glutamate has been another major topic of interest in ischemia. Rapidly after stroke, a massive efflux of glutamate takes place, triggering many changes such as oxidative stress, not only in postsynaptic neurons but also in other cells with glutamate receptors, including pericytes, oligodendrocytes and endothelial cells. Investigations in this direction have been conducted recently on NA-1 to inhibit the NMDA-mediated excitotoxic signalling. By targeting post-synaptic density-95 protein, NA-1 prevents toxic pathways mediated by the neuronal nitric oxide synthase. While these mechanisms had been intensively studied in animal models, including primates, translation into human has not been successful so far. The results however raised the issue of how drug interactions can impair translation of preclinical research into humans, since alteplase (tPA, a thrombolytic drug used after stroke) caused proteolytic cleavage of NA-1, and derivative strategies need to be investigated. Other alternatives have been studied to protect brain cells from glutamate excitotoxicity, such scavenging glutamate from blood using dialysis, based on the idea that glutamate is released from the brain into blood after stroke.

Activation of complement receptors in the vessels endothelium as part of the inflammatory response is yet another mechanism to mention regarding BBB breakdown. The lectin pathway, namely, plays a role in post-ischemic brain damage, with mechanisms such as release of bradykinin that lead to vascular permeability. This provide an interesting target for therapeutic strategies, and studies in animal models showed that inhibition of the lectin pathway or of the C3 activation had protective effects in ischemic stroke.

Therapeutic development and difficulties in translation

From pharmacological strategies to novel therapeutic developments such as exosomes and targeting miRNA responsible for BBB permeability, a major issue remains in translating the preclinical findings from animal models into humans. Beyond reperfusion therapies, there are so far no efficient treatments available to protect the human brain after stroke. There is thus a strong need for novel pipeline designs and instruments to overcome this hurdle. While exploratory research is critical to investigate new ideas, it is important to promote reproduction and validation of these studies through confirmatory research, producing more solid and reproducible data before moving into clinical trials.
There are major methodological issues in the preclinical research trajectory that need to be addressed, and it has been proposed to rethink preclinical studies into more collaborative way, conducting multitrial preclinical studies before actually moving into clinical trials. After individual initiatives at conducting multicentre studies in stroke, NIH started in 2019 the SPAN network, a platform promoting the application of clinical research standards and practices to preclinical studies, to search for new protective strategies in stroke. These ideas were also implemented in the Action plan for stroke in Europe 2018-2030, developing an organisational framework and guidelines that encourage multicentre confirmatory preclinical trials, in order to maximize the success of clinical translation.

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Imaging for vessels and stroke

Prof. Joanna Wardlaw
Univeristy of Edinburgh, United Kingdom

In brain imaging for cerebrovascular diseases, investigation of visible lesions, such as acute infarcts and haemorrhages during stroke, have been the main focus for years. However, with small vessel diseases being known as the cause of about 25% of all stroke and 45% of dementia, other features are being increasingly looked upon, such as white matter hyperintensities, lacunes, holes, microbleeds and perivascular infarcts. For a long time, these were thought to be asymptomatic lesions caused by ischemia and permanent damages putting the patients at a higher risk of stroke.
Since 2013 there has been a change in paradigm regarding these features, with accumulating evidences that they are neither silent, but rather associated with neuropsychiatric and cognitive symptoms that do not fall in the common lexicon of focal stroke neurology, nor permanent. Additionally, cerebrovascular diseases are no longer perceived as “focal” disorders but rather diseases with global effects that can result in remote damages and secondary neurodegeneration.

Recent developments in imaging of cerebrovascular lesions

Advances in the field of magnetic resonance imaging (MRI) have recently allowed to observe sub-visible features, opening the way to more global approaches on cerebrovascular diseases. With high-field systems such as 7T MRI, it is now possible to observe the consequences of these diseases even in small peripheral arterioles, while complementary methods are being developed to detect microinfarcts and investigate white matter tracts.
These growing techniques have fostered important progresses in understanding the features of cerebrovascular diseases. White matter hyperintensities (WMH), for example, is now recognised as a risk factor for stroke, and for many years have been considered to indicate permanent damage aggravating over time. Yet more recent studies highlighted the dynamics of this feature, showing how in about 20% of the patients there was some regression of WMH over one year. Still, the causes of the evolution of WMH remains unknown and is a critical topic for prevention of stroke and dementia.

The topic of perivascular spaces have also been subject to many advances over the last decade, but remains an area of some controversy. High-field MRI have made it possible to observe small vessels in the brain and to assess the presence of perivascular spaces with visual scores that have been instrumental in highlighting the association of higher scores with advancing age, deteriorated cognitive function, vascular dementia, vascular risks and lesions from small vessel diseases. Yet, it is becoming increasingly important to capture features as accurately and quantifiably as possible. For this reason, development of computational measures of the number, size, individual volume and total volume of perivascular space is thus becoming an important priority for imaging on cerebrovascular diseases.
These developments also allow diving into the role of perivascular spaces in other mechanisms, such as clearance of interstitial fluids or formation of WMH. Namely, measures of the size and volume of perivascular spaces showed an important relationship with the severity of WMH (a stronger association than with perivascular spaces count), suggesting that these measurements assess aspects of the perivascular spaces dysfunction more closely related to the formation of WMH. This is an important area of focus for future studies to build understanding of the causes underlying the appearance and evolution of features of cerebrovascular diseases.

Measures of blood brain barrier leakage and vascular dysfunction

In addition, well-characterized quantitative MRI measures are also been developed to assess the differences in brain tissues, including water content and integrity of the tracts, as well as impairments of the blood brain barrier, and in vasoreactivity and vascular pulsatility.

Studies with using gadolinium (a magnetic contrast agent for MRI) have allowed to investigate and quantify the leakage of the blood-brain barrier and to compare different brain regions. This is an important topic since a number of studies on small vessel diseases and dementia suggested a leakage through the blood brain barrier, which increases with age and other risk factors and is aggravated in patients with severe WMH and enlarged perivascular spaces. Data suggests that the severity of blood brain barrier leakage actually predicts worsening cognitive decline and functional outcomes after small vessel stroke. Imaging in CADASIL and sporadic small vessel diseases highlighted focal areas of leakage, particularly at the edges of lacunes, microbleeds and WMH, suggesting a more complex vascular dysfunction in these areas. However, observation of the leakage is based on techniques that remains difficult to be applied in the multi-centred studies with large sample size that are necessary to capture the diversity of the population in terms of vascular function, and methodological barriers are to be addressed for better homogenization.

Additionally, recent imaging developments also allow to dive into other vascular dysfunction, with standardized ways to investigate vasoreactivity and vascular pulsatility in the brain, namely in small vessel diseases. This allowed to highlight a decline in vasoreactivity to CO_2 associated with increased WMH and perivascular spaces volumes, as well as clusters of dilated vessels in abnormal white matter in small vessel diseases that may reflect chronically dilated vessels and sites of lacunes formation.

Next stages of imaging development

There have been promising advances regarding imaging in cerebrovascular diseases, and these techniques can be further leveraged, as seen for example in MRI studies investigating the brain lymphatic system suggesting CSF drainage into the paranasal and meningeal lymphatics. Fluid movements and waste clearance systems in the brain are topics in need for more focus, with strong interrelation with other areas such as blood brain barrier function and age, and it is important to encourage such developments.

Yet a number of difficulties remains in using these developing methods due to subtleties of the lesions involved in cerebrovascular diseases. Computational analysis namely requires further improvements in quantitative tools to allow developing fast and accurate methods that can deal with the larger sample sizes. Additionally, it is important to foster robust multimodal approaches to investigate these disorders in terms of a combination of several vascular dysfunctions simultaneously. Lastly, quantitative biomarkers have proved to be valuable tools and it is important to support progresses in this direction.

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New technologies in cerebrals vessels

Prof. Netanel Korin
Technion - Israel Institute of Technology, Haifa, Israel

Recent technological advances have allowed for promising approaches in terms of both basic and clinical research on cerebrovascular diseases. It is key to acknowledge and foster such progresses to help build a better understanding of these diseases and better therapeutic strategies.

In vitro disease models

The neurovascular unit is a complex structure involving interactions of different cell types, and there is a critical interest in building the understanding on these interactions to develop better treatments. While in vivo models have been instrumental in this regard, providing instructive data, translation has been an ongoing hurdle in the field, possibly due to the important differences in the physiological and pathological mechanisms in animal models and in the human brain. Three-dimensional in vitro disease models could thus prove an efficient tool to overcome the challenges, thanks to the ongoing progresses in the field of microfluidics and lab devices. It is now possible to complement in vivo results with work in controlled conditions, and more and more studies show uses of organoid chips and in vitro microphysiological systems that replicate aspects of the blood brain barrier in normal or diseases conditions, highlighting an increasing relevance of these models to study neurovascular diseases.
Among the models of interest for the field, the membrane-based barrier models rely on a membrane separating the vascular and tissue areas on a chip to model the brain vasculature. By coupling chips, it is even possible to look at the communication between the models, as illustrated in a 2018 study by Maoz looking into the metabolic coupling of endothelial and neuronal cells. These models can even be further enhanced to be more physiologically relevant, for example by including a period of differentiation under hypoxic conditions, providing new tools to develop and validate drug delivery approaches.
Additionally, self-assembled models have been widely used to investigate the blood brain barrier function: based on iPS cells assembled over time in a hydrogel medium, they are more physiologically relevant models. Furthermore, they allow for a more controlled monitoring of the physiological and pathological mechanisms throughout the experiment, namely with imaging and permeability measurements.
There is currently a gap in science regarding the blood-brain interface that need to be addressed, and it is important to foster work in this interdisciplinary field, that can promote new approaches for understanding and treating cerebrovascular diseases. In vitro models can thus prove instrumental not only regarding the blood brain barrier but also for diseases of larger vessels such as aneuvrism, where tissue engineering has allowed for increased work on 3D-printed vessels models that could even account for blood flow.

Nanomedicine and targeted drug delivery

While cerebrovascular diseases are global, they may have local attributes such as embolism, brain haemorrhage and cerebral aneuvrism, and there is thus an advantage in providing focal treatment of these attributes. Targeted drug delivery would thus prove of great interest for these conditions, especially regarding tPA and other drugs with severe side effects outside of the site of action. The question of balancing safeness and efficiency when using thrombolitic drugs for treatment of ischemic

stroke is indeed crucial, since side effects can cause further damages in later stages (brain haemorraghee, brain edema and blood brain barrier leakage).
Usage of nanomedicine for thrombolitic drugs targeted delivery is decades old, and it is important to foster advancements in carriers formulation. Some recent work have been focused on developping deformable long-circulating carriers for tPA, allowing for longer acting treatments while showing similar efficiency as tPA alone. Other strategies involved local delivery of lesser amount of drug to reduce the side effects. This include studies focused on coupling affinity molecules with the carriers, with namely clot-responsive carriers formed of cell-mimetic nanovesicles inspired from platelets, and other relying on carriers responsive to endogenous stimuli (from enzyme-responsive to mechanical-responsive carriers that break in presence at the sthenotic area).

The rising field of nanomedicine for targeted delivery has also showed benefits in addressing several gaps in medicine regarding treatments of cerebrovascular diseases, opening the way for new approaches.
As mentioned, targeted delivery has a potential to change the pharmacokinetics of the drugs, raising interesting questions regarding the time window for treatment in stroke. It is well known how the delay between the onset of embolic stroke and treatment is critical to avoid brain damage, yet current treatments require transportation of the patient to the hospital and imaging, adding to the delay of treatment. An option to change the care paradigm would be to explore for safer and longer acting thrombolysis treatments that are not as efficient as tPA, that could be used as to administer as first aid for very early interventions to prevent brain damages.
Lastly, there is another important gap regarding the combination of pharmacological approaches with other treatment strategies. There is a recent illustration on thrombectomy, an efficient mechanical approach, that however have problems due to the increased risk of distal embolies caused by fragments of the main thrombus. Drug carriers targeting these distal clots can prove very useful here in reducing the risks of this intervention, and this prompt to foster more the joint development of drugs and devices for treatments of cerebrovascular diseases.

Devices for drug-free interventions in aneurysm

Technological innovations have also benefited to drug-free interventions, with devices development revolutionizing intraarterial treatments of large vessels. This is especially the case for cerebral aneurysm, a disorder that is quite common, but the very low risk and rupture (5%) yet high mortality in case of rupture (over 50%) raising questions on whether to intervene or not.
Devices are becoming more and more used as therapeutic strategies for cerebral aneurysms, namely stents for flow diverting and coiling devices, thanks to improvements in expandable implants for a better placement of the device in the aneurysm cavity. Yet, important challenges remains in the field of biomaterials, since metallic implants raise issues on healing and may require antiplatelet medications. While one approach in this regard is to replace metallic parts with biomaterials, promising work has also been done on injectable biomaterials that would harden to fill the aneurysm cavities.
On a methodological note, there is a need to investigate strategies to detect aneurysms with higher risk of rupture, in order to provide better guidelines on whether intervention is required or not.

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Rehabilitation and compensatory mechanisms for cerebrovascular diseases

Prof. Andreas Luft
Stroke Center, University Hospital of Zurich, Switzerland

Investigations on the rehabilitation mechanisms involved to overcome deficits caused by cerebrovascular diseases have benefited in the last 20 years from the knowledge in brain plasticity and regeneration, allowing to identify two conceptually different approaches.
On one hand, true neurological recovery relies on the reconstruction of functional circuits and the recruitment of previously silent circuits in non-damaged areas to compensate for the lesions. On the other hand, compensation is an approach based on other body structures being involved in overcoming the deficit caused by the lesions, such as trunk displacement to make up for lower movement range of the arm.
While compensation comes faster and allow the patient independence after the disease acute phase, the resulting suboptimal movement quality present disadvantages in terms of energy cost and long-term pain, spasticity and orthopaedic complications. For this reason, while compensation is very important in the early stages of rehabilitation, it shall later decrease as neurological recovery progresses.

Motivation as a key factor of recovery and compensation

While it remains unclear which movement training methods prioritize neurological recovery or compensation, active training is undoubtedly the central strategy in the rehabilitation process. Several studies demonstrated the role of motivation in successful therapies, with a clear correlation between internal motivation scores and changes in the Function Independence Measure during the rehabilitation period.
This is especially relevant in stroke, since mice and MRI studies showed evidences of deficits in the dopaminergic system leading to a complex syndrome called post-stroke depression, that is associated with lack of motivation and lack realisation of one own improvements. There are indeed dopaminergic neurons that project directly into the primary motor cortex, and damages in this system impairs motor task learning but not performing an already-learnt task. Indeed, dopamine is necessary in the primary motor cortex for long-term potentiation (LTP), a form of synaptic plasticity that drive the healthy motor learning. All these observation led to the development of strategies pairing levodopa with motor training after stroke, and while initial results showed better outcomes in movement scores with faster recovery, more clinical trials are ongoing that try to reproduce and validate this approach.
Alternatively, several studies investigated the effect of other forms of stimulation to improve the patient's motivation. The Armeo Senso Reward trial (Widmer et al, 2021), for example, looked at the influence of rewarding games (with in-game feedback) and money rewards on arm training, showing significant improvements in functional and impairment scores. Furthermore, not only does rewarded training improve the outcomes during the initial therapy but also during the follow-up period, suggested that highly motivated patients continue to improve and practice in daily life.

Training consolidation

Another important part of the training is actually its consolidation, outside of the training sessions. Numerous studies on learning are highlighting the essential role of sleep in this regard, with strategies to improve consolidation (such as resorting to similar contexts for learning and consolidation) that can be translated to stroke recovery. Investigating context cuing, in the form of music or odours, for post-

stroke arm movement training showed not only improved performances in the training itself but also better outcomes in terms of movement recovery. This emphasizes how interventions acting on environmental factors can have important benefits on existing therapeutic interventions.

Timeframe of intervention for better rehabilitation

It is important to note that the different movement features monitored after stroke have different time profiles of recovery, as for example coordination impairments recover between 1,5 and 5 weeks after stroke while biceps strength continues to improve after more than 14 weeks. This is conceptually very important for rehabilitation strategies, and even more as there might be time when recovery is optimized by mechanisms induced by the lesion. Investigation in rat models for stroke indeed showed that LTP is facilitated 14 days after the stroke onset, pinpointing a potential time window of enhanced plasticity that may also exist in humans.

This situation is further illustrated by investigation of anti-nogo A administration in rat models combined with motor training, with consecutive interventions (anti-nogo A followed by training) showing far better results than simultaneous ones. Timing is thus very relevant for rehabilitation strategies, and ensuring that active training falls in periods of plasticity would improve its beneficial effects for neurological recovery and compensation.

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Panel discussion with representatives of European patient's organizations

Arlene Wilkie and Anita Arsovska, Stroke Alliance For Europe (SAFE)
Rubina Ahmed, Stroke Association UK

The Foresight symposium was concluded by a panel discussion with representatives of Stroke Alliance For Europe and Stroke Association UK, providing a patient view on the research on stroke and blood-brain barriers and pointing the necessary efforts necessary to improve the lives of patients and stroke survivors.

Cerebrovascular diseases, including stroke, are known as serious life-threatening conditions with a high prevalence. However, research in this area is heavily underfunded in comparison with other conditions with similar prevalence and burden. It is thus key to build capacity in research on cerebrovascular diseases and to make the best of the resources available.

Organizations such as SAFE have been strongly involved in identifying the research priorities that could prove the most beneficial for the patients. The first topic to stand out in this regard is prevention, and namely the identification of risk factors, other than the common life habits factors. Basic research plays an important role in this area that patients acknowledge, and development of biobanks is key for the future. The second main priority is life after stroke, a central concern for patients, and we need to encourage investigations on new technologies and new methods to improve the rehabilitation after stroke and other cerebrovascular diseases.

The discussion also highlighted the importance of holistic approaches to take comorbidities into account. Cerebrovascular diseases are often associated with other conditions such as diabetes or hypertension, and it would be very beneficial to treat patients as a whole rather than having specialists treating each condition separately. This global approach would not only benefits for treatments, but also for other aspects such as prevention. Due to the important overlaps in both the care and prevention strategies for coexisting conditions, developing joint strategies would lead to far better outcomes.

Considering comorbidities is also critical for preclinical research, with translation being a major hurdle for research on cerebrovascular diseases. The development of more complex animal models has been highlighted as a potential answer to this challenge, and models that allow investigating multiple risk factors simultaneously could be instrumental in this regard.

Lastly, it is important to set the ground for future developments, so that advances in basic research can reach the clinical practice and the patients more efficiently. There is indeed a strong need to develop guidelines for research, treatments and health practices, so that efforts from the scientific community can have a better impact on patients' lives in all countries. The Stroke Action Plan for Europe (SAP-E), developed by the European Stroke Association in collaboration with SAFE, illustrates the kind of large international initiatives that are needed to tackle cerebrovascular diseases.

Annex

List of attendants

Speakers

Rubina Ahmed	Stroke Association UK
Anita Arsovska	Stroke Alliance For Europe (SAFE)
Martin Dichgans	Institute for Stroke and Dementia Research, Ludwig-Maximilians-Universität, Munich, Germany
Andreas Luft	Stroke Center, University Hospital of Zurich, Switzerland
Netanel Korin	Technion - Israel Institute of Technology, Haifa, Israel
Anna Maria Planas	Institute for Biomedical Research of Barcelona (IIBB) - Spanish National Research Council (CSIC), Barcelona, Spain
Steven Proulx	Theodor Kocher Institute, University of Bern, Switzerland
Élisabeth Tournier-Lasserve	Lariboisière Hospital, University of Paris, France
Joanna Wardlaw	Univeristy of Edinburgh, United Kingdom
Arlene Wilkie	Stroke Alliance For Europe (SAFE)

Guests

Tine D'aes	Liège University, Belgium
Monica Ensini	European Commission, Research and Innovation Directorate-General, Belgium
Katja Grossmann	German Research Foundation (DFG), Bonn, Germany
Liga Zvenjniece	Latvian Institute of Organic Synthesis, Latvia

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