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Session 2: Biomedical discoveries, preventive/therapeutic strategies and the risks

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Franco Maria Buonaguro

Introduction – **Presentation Slides**

Biomedical discoveries in the preventive and therapeutic fields have been significant and frequent over the past 50 years. Have they been risk-free? The latest COVID experience is the most recent we have all witnessed. Although the COVID pandemic appears to be over, with the exception of some still unresolved questions related to long COVID, the two main aspects that continue to intrigue the scientific community are (a) the potential role of laboratory manipulations as a source of a highly pathogenic SARS-CoV-2, and (b) the amyloidogenic role of the virus's spike protein and even the recombinant spike protein expressed by the recently developed mRNA vaccine. Furin plays a role in both. Furin is the first human proprotein convertase (PC), identified in 19861. It is widely distributed in all human tissues and involved in various metabolic and pathological processes, including the maturation of over 150 proproteins, particularly virtually all hormones and neuropeptides2,3. Furin is also exploited by viruses to increase transmission efficiency and viral tropism4,5. In addition to the COVID pandemic and strategies to contain it, this session reported and discussed new developments in neurodegenerative and neurocognitive diseases, as well as rheumatological diseases and rare cancers such as Burkitt's lymphoma. We must improve our preparedness for potential new epidemics, as highlighted by Ishwar Gilada, but we must also contain the risks associated with our technologies, as warned by Per Hammarström.

Massimo Ciccozzi

The Spike and the FCS evolution in Coronaviruses → **Presentation Slides** -

In the last years several studies have been performed on the evolutionary processes of the SARS-CoV_2, have identified and characterized the unique presence of the PRRA Furin Cleavage Site (FCS), which is absent in other known Sarbecorvirus (lineage B beta Coronaviruses) 5-8. Although it is possible a rare recombination event between the SARS-CoV-2 and other human Coronaviruses prevalent in the rino-pharyngeal tract, which often carry such FCS (in particular the two human Alphacoronavirus, NL63 and 229E), a laboratory engineered manipulation has been suggested to increase the pathogenicity, by a gain of function strategy, in order to establish an in vivo model based on humanized mice. Dr Ciccozzi presentation has been focused on the key dilemma of a natural zoonotic evolution from mammalians with an ACE2 receptor homologous to the humans or a laboratory engineered recombinant virus. The key issue is the presence of the PRRA Furin Cleavage site (FCS), not present in the SARS-CoV_1 (the Urbani strain of 2003) and not present in other Sarbecorvirus strains. Several Sarbecorvirus (lineage B beta Coronaviruses) have proteolytic cleavage sites at the S1/S2 boundaries and the S2 NH2 terminal sensitive to other proteases, i.e. the TMPRSS2, which is however not highly diffuse as for the Furin in human tissues8. Furin cleavage sites are in the genera AlphaCoronavirus and

Gammacoronavirus as well as in other subgenera of the Betacoronavirus such as Merbecovirw; and Embecovirus, with peculiarities which suggest a different evolutionary process.

Finally, it should be mentioned that Furin cleavage is critical to many viral diseases, including HIV, Ebola, and influenza H5 and H79. Furin is a ubiquitously expressed protease in human body, with a wider distribution range than the major protease responsible for cleaving spike, TMPRSS2. Therefore, coronaviruses with spike containing furin cleavage site may have advantage in spreading8. In conclusion, for all such reasons, although at the moment there is not a final prove of human manipulation, all such anomalies strongly favor a human role. The obvious final question, if the active role of humans were demonstrated, would be whether it was simply a laboratory error or a conceptual error in failing to evaluate all the potential risks of a gain-of-function activity. To resolve this question, the project approved and funded by the NIH would need to be analyzed in detail to verify whether this strategy was already a goal of the project and had in fact also been approved by the U.S. funding agency.

Sofie Nyström

Amyloidogenic peptides → **Presentation Slides**

Prof Nyström focused on proteins, as the working horses of life and essential for all life forms. The function of a protein is dependent on its unique three-dimensional shape, the native fold. However, proteins can also undergo a shape-shifting misfolding process and sometimes this leads to the formation of amyloid protein structures. An amyloid is s threadlike structure that is composed of many protein molecules held together by intermolecular interactions. These amyloid fibrils are notorious for their ability to recruit more of neighbouring proteins into the amyloid state and for causing a multitude of disease in humans. Neurodegenerative diseases such as Alzheimer's disease and Parkinsons disease are examples of such amyloid dependent diseases. Although the mechanism of amyloid formation is similar between several amyloid diseases, they are coupled to the misfolding, and amyloid formation of distinct proteins and the symptoms of the disease are different.

Both in the case of Alzheimer's disease and Parkinson's disease there are known genetic mutations in the culprit protein, rendering a protein that is more prone to misfold into the aberrant amyloid state. Such mutations account for 5-15% of all cases of Alzheimer's and Parkinson's disease. The direct cause of the rest, the overwhelming majority of all disease cases is not known, although several risk factors have been identified. Both viruses10 and bacteria11 are known to contain amyloid-forming proteins that in many cases play a functional role for the microbe. Epidemiologic studies provide an insight to virus infections as a driving force for neurodegenerative disease12,13 and it was recently established that vaccination against Herpes Zoster gives some protection also against dementia14,15. Bacterial amyloids have been shown to provoke amyloid formation of the Alzheimer's disease associated protein Aβ Parkinson's disease associated protein α-synuclein16,17.

Experiments conducted on virus derived proteins in the test tube, from both SARS-CoV-2, Influenza A and Herpes Simplex demonstrate their potential to form amyloid structures. Furthermore, adding such preformed amyloids of virus proteins to human proteins involved in Alzheimer´s and Parkinsons disease results in acceleration of the disease associated misfolding of the human proteins18 and Nyström et al unpublished. Epidemiologic evidence and laboratory experiments in concert lead to the conclusion that it is worth to follow the trail of viral and bacterial infections to find the root cause and potentially a strategic point for combating neurodegenerative disease that are devastating many lives world-wide.

Emanuele Buratti

TPD-43 misfolding and SLA → **Presentation Slides**

The SISMIC-TDP43 project focuses on the TAR-DNA binding protein (TDP-43), an amyloidogenic protein implicated in the pathogenesis of Amyotrophic lateral sclerosis (ALS). TDP-43 is a 414 amino acid nuclear protein, and its misfolding and accumulation in the cytoplasm are recognized hallmarks of ALS and FrontoTemporal Lobar Degeneration (FTLD). ALS is characterized by the progressive loss of motor neurons, while FTLD involves the deterioration of frontal and temporal lobes, causing behavioral changes and language impairment. Current therapeutic strategies have failed to effectively and specifically target the structural transitions of TDP-43, often relying on non-specific approaches like increasing clearance or preventing phosphorylation. To address this problem, the SISMIC-TDP43 project, which stands for Structure based Identification of Small Molecules Interacting with and Counteracting TDP-43 aggregation, aims to bridge this therapeutic gap. Its objective is to discover, synthesize, and validate small molecules designed to bind to TDP-43. The molecules adopt a dual approach: either stabilizing physiological TDP-43 dimers or preventing and reversing pathological aggregates, thereby restoring protein function. Small molecules are preferred due to their chemical versatility, tractable pharmacology, and potential for brain penetration. The project employs five interconnected aims to systematically identify and validate candidate therapeutics and diagnostic imaging tools. These aims include: Proteochemometrics (Aim 1) that consists in mapping the full TDP-43 CTD pocketome to detect approximately 23,700 potential sites and facilitate drug repurposing by comparing them with pockets in the Protein Data Bank (PDB); Virtual Screening (Aim 2) that utilizes an AI-driven Large Scale Virtual Screening Pipeline to explore chemical space. This massive effort involves identifying binding sites using the InDeep neural network and docking libraries, including the EnamineREAL database containing up to 36 billion compounds; Peptidomimetics (Aim 3) for the design and synthesis of peptide analogues to interfere with the aggregation process; and In Vitro Assays (Aim 4) to characterize the binding affinity and aggregation interference efficacy using advanced biophysical methods, such as ThT fluorescence and electron microscopy (EM). Finally, the project will include interactions with the Biology (Aim 5) to validate efficacy in cellular models against aggregation, clearance, nuclear localization, and splicing regulation, leading to the selection of both candidate therapeutics and PET tracers. To this date, preliminary results have led to the identification of four candidate molecules. All four molecules demonstrated a positive effect by reducing TDP-43 aggregation, a result confirmed through both ThT fluorescence monitoring and supporting electron microscopy images. In conclusion, this data has contributed to defining the TDP-43 CTD pocketome and yielded first-generation small molecules that inhibit or reverse TDP-43 aggregation, alongside initial candidate diagnostic tracers necessary for monitoring ALS.

Felice Iasevoli

Misfolding in neurodevelopmental and neurodegenerative disorders → **Presentation Slides**

Felice Iasevoli's presentation focused on the association of the reduction of Furin activity with neurodegenerative (i.e. Alzheimer's Disease) and neurocognitive (i.e. Schizophrenia) diseases. If increase of proteins and peptides with amyloidogenic properties have been shown to play a major role in older-age neurodegenerative disorder, including Parkinson and Alzheimer's Disease, neurodevelopmental disorders, in particular autism spectrum of disorders (ASD) and Schizophrenia (SCZ) have been associated with the reduction of Furin expression and the consequent reduction of Brain-derived neurotrophic factor (BDNF), relevant for the dendritic prunic involved in the maturation of neuronal connections19.

FURIN is a prototypical member of the proprotein convertase (PCSK) family, a group of subtilisin-like serine proteases responsible for converting a wide range of inactive precursors into their biologically active forms. This enzymatic activation represents a key post-translational regulatory step across numerous physiological systems. FURIN's substrates include more than 150 precursor proteins, encompassing hormonal peptides,

growth factors, receptors, and neuropeptides20,21. Among the best characterized are proinsulin, cleaved to insulin22; pro-ACTH and pro-vasopressin, converted into their active neuropeptide forms23,24; and various substrates implicated in neuroendocrine communication and homeostatic regulation. Within the central nervous system, FURIN plays an equally pivotal role. It is highly expressed in neurons and glial cells, where it controls axon guidance, neuronal migration, and synaptic maturation. Among its most relevant neurobiological functions is the cleavage of proBDNF into mature BDNF, a process essential for maintaining appropriate levels of synaptic pruning, dendritic arborization, and network plasticity20. Proper maturation of BDNF is indispensable for experience-dependent refinement of cortical and subcortical circuits, particularly during adolescence and early adulthood—a developmental window crucial for the establishment of cognitive and affective functions. Defective FURIN activity disrupts this delicate equilibrium. Reduced conversion of proBDNF leads to an excess of its unprocessed form, which preferentially binds to p75NTR receptors, triggering apoptotic and anti-synaptogenic pathways. This shift from trophic to atrophic signaling is thought to underlie altered synaptic density, impaired excitatory–inhibitory balance, and dysfunctional network connectivity, all of which are recognized hallmarks of schizophrenia, autism spectrum disorders (ASD), and other neurodevelopmental syndromes.

Recent genomic and transcriptomic studies have confirmed the presence of both common and rare variants in the FURIN gene that modulate expression and enzymatic efficiency. One key regulatory element is the rs4702 SNP within the 3′-UTR region, which affects the binding of microRNA miR-338-3p25. The G allele of this variant weakens miRNA binding, reducing FURIN translation and subsequently diminishing the availability of mature BDNF. The result is a cascade of neurobiological effects involving impaired synaptic signaling, dendritic simplification, and cortical dysconnectivity. Furthermore, converging evidence from post-mortem and animal studies supports a dimensional view of psychiatric nosology, where FURIN dysregulation contributes to a shared molecular vulnerability that spans from autism to schizophrenia. The gradient of FURIN activity may influence not only the degree of cortical pruning but also the timing of critical neurodevelopmental events, thereby determining the specific clinical phenotype along this continuum.

Beyond its molecular and developmental roles, FURIN's pharmacological relevance is gaining increasing attention. A number of FURIN inhibitors are currently being explored as antiviral and anticancer agents, exploiting its role in processing viral glycoproteins and tumor-associated growth factors26. However, given FURIN's pleiotropic functions in the brain, systemic inhibition might pose neuropsychiatric risks—particularly in individuals with preexisting genetic or epigenetic vulnerability leading to reduced FURIN functionality. In such subjects, further suppression of FURIN activity could theoretically precipitate acute neurocognitive disturbances, behavioral disinhibition, or even neuroinflammatory sequelae. This consideration emphasizes the need for careful safety evaluation and translational research, integrating molecular pharmacology with neurodevelopmental and neuropsychiatric expertise.

Overall, FURIN represents a biological and pharmacological intersection point between infectious disease, oncology, endocrine regulation, neurotrophic signaling, and brain architecture integrity, relevant to both neurodevelopmental and neurodegenerative diseases. Its balanced activity ensures the proper maturation of neuropeptides and growth factors, sustaining the dynamic equilibrium between synaptic formation and elimination that underpins higher-order cognition. Dysregulation of this system—whether genetically, epigenetically, or pharmacologically induced—may constitute one of the core mechanisms linking neurodevelopmental and neurodegenerative disorders.

Neal S. Young

Somatic Mutations in VEXAS syndrome → **Presentation Slides**

Neal S. Young described the new VEXAS syndrome caused by somatic mutations in the UBA1 gene, which is located on the X chromosome. The initial description, from NIH with Young contributing, was published on NEJM in 202027 and many publications have followed28-30. The mutations in the UBA1, located on the X

chromosome, are acquired (non-hereditary) and occur during a person's lifetime specifically in the hematopoietic stem and its progenitor cells. The most common mutation is at the methionine 41 (Met41) position, with specific variants like Met41Thr, Met41Val, and Met41Leu being most frequent. This mutation affects the E1 enzyme's function, leading to systemic inflammation and features of autoinflammatory diseases.

The name VEXAS is an acronym deriving from the core features of disease: V: Vacuoles are often identified in the bone marrow stem cells of patients presenting with VEXAS; E: The E1 ubiquitin conjugating enzyme encoded by the UBA1 gene is mutated in patients; X: The mutated UBA1 gene is recessive and located on the X-chromosome and thus the disease is almost exclusively found in individuals with a single X chromosome and thus said to be X-linked; A: Patients with VEXAS present with a wide array of autoinflammatory conditions; S: The mutations which cause VEXAS are somatic: they are acquired throughout life, not inherited, and are not passed on to offspring. The frequency of the mutation is not rare with 1 case in 13 591 unrelated individuals (95% CI, 1:7775-1:23 758): 1 in 4269 men >50 years (95% CI, 1:2319-1:7859) and 1 in 26 238 women older than 50 years (95% CI, 1:7196-1:147 669); macrocytosis of red blood cells and anemia appear to be early signs; the disease is not uncommon among older, usually Caucasian men31.

The treatment is still not defined and standardized but includes high doses of corticosteroids, Ruxolitinib (and other jak inhibitors), Tocilizumab (anti-IL6R), Azacytidine. Hematopoietic stem cell transplant is curative but carries risks of morbitidy and mortality.

Moreover, Young described several non -oncological conditions characterized by somatic mutations, such as endometriosis32,33, and possibly brain diseases including autism34 and schizophrenia35,36. This discovery opens a totally new field not only benign and malignant cancers are associated to genetic changes, but also inflammatory conditions (including rheumatological auto-immune disease) associated to genetic changes which could generate protein's changes, perhaps able to induce an immune response against a modified self and by other still uncertain mechanisms.

Sam Mbulaiteye

The EBV role in human diseases and current vaccine efforts → **Presentation Slides**

Sam Mbulaiteye in his presentation recapitulate the information on the EBV role in human diseases and in particular in Burkitt Lymphoma, a very peculiar cancer in sub-Saharan young children, characterized by jaws involvement. Sam, in 2010 established and since then coordinated a very unique study in 3 sub-Saharan countries (Kenya, Uganda and Tanzania) funded by NIH: the EMBLEM project, an Epidemiology of Burkitt Lymphoma in East African Children and Minors study to assess the relationship between coendemic Malaria and the pediatric Endemic Burkitt lymphoma (eBL) in sub-Saharan Africa37. Previous cross-sectional studies of limited geographic areas have not found a convincing association. The scientists involved in the project used spatially detailed data from the EMBLEM study to assess this relationship. EMBLEM is a case-control study of eBL from 2010 through 2016 in six regions of Kenya, Uganda, and Tanzania. To measure the intensity of exposure to the malaria parasite, Plasmodium falciparum, among children in these regions, we used high-resolution spatial data from the Malaria Atlas Project to estimate the annual number of P. falciparum infections from 2000 through 2016 for each of 49 districts within the study region. Cumulative P. falciparum exposure, calculated as the sum of annual infections by birth cohort, varied widely, with a median of 47 estimated infections per child by age 10, ranging from 4 to 315 infections. eBL incidence increased 39% for each 100 additional lifetime P. falciparum infections (95% CI: 6.10 to 81.04%) with the risk peaking among children aged 5 to 11 and declining thereafter. Alternative models using estimated annual P. falciparum infections 0 to 10 y before eBL onset were inconclusive, suggesting that eBL risk is a function of cumulative rather than recent cross-sectional exposure. Their findings provide population-level evidence that eBL is a phenotype related to heavy lifetime exposure to P. falciparum malaria and support emphasizing the link between malaria and eBL38. Moreover, the EMBLEM studies on one of the largest sample collections

allowed several molecular studies, including Next generation sequencing, with the identification and characterization of EBV Variants39 and genetic susceptibility to recurrent or chronic infection by Epstein-Barr virus or Plasmodium falciparum40.

EBV Variants: Epstein-Barr virus (EBV) infection, a ubiquitous infection, contributes to the etiology of both Burkitt Lymphoma (BL) and nasopharyngeal carcinoma, yet their global distributions vary geographically with no overlap. Genomic variation in EBV is suspected to play a role in the geographical patterns of these EBV-associated cancers, but relatively few EBV samples from BL have been comprehensively studied. We sought to compare phylogenetic patterns of EBV genomes obtained from BL samples in Africa and from tumor and non-tumor samples from elsewhere. We concluded that EBV obtained from BL in Africa is genetically separate from EBV in Asia. Through comprehensive analysis of nucleotide variations in EBV's LMP-1 gene, we describe 12 LMP-1 patterns, two of which (B and G) were found mostly in Asia. Four LMP-1 patterns (A, AB, D, and F) accounted for 92% of EBVs sequenced from BL in Africa. Our results identified extensive diversity of EBV, but BL in Africa was associated with a limited number of variants identified, which were different from those identified in Asia. Further research is needed to optimize the use of PCR and sequencing to study LMP-1 diversity for classification of EBV variants and for use in epidemiologic studies to characterize geographic and/or phenotypic associations of EBV variants with EBV-associated malignancies, including eBL41.

Genetic susceptibility to recurrent or chronic infections: Burkitt lymphoma (BL) is responsible for many childhood cancers in sub-Saharan Africa, where it is linked to recurrent or chronic infection by Epstein-Barr virus or Plasmodium falciparum. However, whether human leukocyte antigen (HLA) polymorphisms, which regulate immune response, are associated with BL has not been well investigated, which limits our understanding of BL etiology. Here we investigate this association among 4,645 children aged 0-15 years, 800 with BL, enrolled in Uganda, Tanzania, Kenya, and Malawi. HLA alleles are imputed with accuracy >90% for HLA class I and 85-89% for class II alleles. BL risk is elevated with HLA-DQA1*04:01 (adjusted odds ratio [OR] = 1.61, 95% confidence interval [CI] = 1.32-1.97, P = 3.71 × 10-6), with rs2040406(G) in HLA-DQA1 region (OR = 1.43, 95% CI = 1.26-1.63, P = 4.62 × 10-8), and with amino acid Gln at position 53 versus other variants in HLA-DQA1 (OR = 1.36, P = 2.06 × 10-6). The associations with HLA-DQA1*04:01 (OR = 1.29, P = 0.03) and rs2040406(G) (OR = 1.68, P = 0.019) persist in mutually adjusted models. The higher risk rs2040406(G) variant for BL is associated with decreased HLA-DQB1 expression in eQTLs in EBV transformed lymphocytes. Our results support the role of HLA variation in the etiology of BL and suggest that a promising area of research might be understanding the link between HLA variation and EBV control40.

Ishwar Gilada

Alternative strategies to prevent/cure global virus-induced diseases. → **Presentation Slides**

Ishwar Gilada in his presentation discussed the need for new strategies to combat viral outbreaks and future pandemics, as traditional tools like vaccines and antiviral drugs are not enough on their own. It emphasizes exploring innovative, scalable, and globally inclusive strategies.

- Preventive Strategies: To better prevent and manage future pandemics, we must explore alternative and complementary strategies that are innovative, scalable, and globally inclusive (replicability, adaptability and accessibility). These include developing universal vaccines, using genetic engineering to build resistance, employing AI and genomics for viral bio-surveillance, enhancing the microbiome, utilizing antiviral surfaces and air filtration, and adopting a "One Globe-One Health" framework that connects human, animal, and environmental health.
- Curative / Therapeutic Strategies: Advances in this area include broad-spectrum antivirals, RNA-based therapies, engineered immune cells, and repurposing natura*l compounds offer new hope.

- Systemic and Infrastructure Strategies: Multi-faceted strategies can help focus on building a more resilient public health system through decentralized manufacturing platforms, digital health and early warning systems, and global coordination via a pandemic treaty.

In conclusion, the lessons from past pandemics underscore the urgent need for global preparedness, proactive strategies, and collective action. Emerging threats like HPV, HBV, and AMR highlight the necessity of alternative approaches alongside conventional methods. Embracing innovations such as universal vaccines, broad-spectrum antivirals, RNA-based therapies, nanotechnology, and AI can revolutionize our pandemic response. Central to success are robust systems for pathogen tracking, genome sequencing, and global knowledge sharing. Ensuring health security requires integrated disaster management and a unified "One World–One Hope" vision, grounded in environmental respect and preventive action.

Per Hammarström

The brave new world of biologic drugs - safe and effective? → **Presentation Slides**

Per Hammarström's talk conveyed both enthusiasm and concern regarding the rapid development of biopharmaceutical drugs, also known as biologics. Biologic drugs are at the forefront of modern medicine, enabling the treatment of previously intractable diseases. Biopharmaceuticals encompass synthetic, semisynthetic, and recombinant peptide and protein drugs, as well as oligonucleotide-based agents, including modified messenger RNAs (mRNA), small interfering RNAs (siRNA), and antisense oligonucleotides (ASOs)42.

According to Pharmaceutical Research and Manufacturers of America (PhRMA) (https://phrma.org/), more than 7,000 biopharmaceutical products are currently in clinical development worldwide, with over 1,000 having reached Phase 3 trials. Additionally, more than 100 non-COVID-19 monoclonal antibody (mAb)-based products are in late-stage clinical development. The global biopharmaceuticals market was valued at USD 616.94 billion in 2024 and is projected to grow from USD 666.41 billion in 2025 to USD 1,183.87 billion by 2032 (https://www.fortunebusinessinsights.com/biopharmaceuticals-market-106928).

However, the rapidly expanding and increasingly accessible biopharmaceutical landscape also presents risks. Proteins are labile molecules, and amyloidosis refers to a group of conditions in which proteins misfold and assemble into stable fibrillar structures with a strong tendency to grow and replicate by recruiting additional proteins into the misfolded form, which can have very detrimental effects in the organs where it occurs.

Dr. Hammarström demonstrated that the essential diabetes drug insulin is highly amyloidogenic - a property that has been known for a long time43. More recently, the highly successful glucagon-like peptide-1 (GLP-1) agonists, such as semaglutide (Wegovy®, Ozempic®), which are now widely used for both diabetes and weight loss, have been shown to be highly amyloidogenic. Similar properties have been observed in other peptide drugs, such as enfuvirtide (Fuzeon®) used against HIV44. The potential long-term effects of localized iatrogenic amyloidosis resulting from such treatments remain unknown.

Even more concerning is the emergence of mRNA-based biologics, which use the human body as a platform to express novel - and in many cases, exotic - proteins. This was exemplified by the mRNA COVID-19 vaccines, which instruct cells to produce the SARS-CoV-2 spike protein. The spike protein itself has been shown to be highly amyloidogenic under immune-reactive conditions45 (Nyström and Hammarström 2022). Because the mRNA is delivered via lipid nanoparticles that can distribute systemically, there is potential for expression in a wide range of cells and organs, raising concerns about the possibility of systemic amyloidosis in susceptible individuals. The long-term risks of adverse events, such as amyloidosis, are not yet sufficiently considered in the rapidly evolving field of biologic drug development.

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