ACCADEMIA NAZIONALE DEI LINCEI

Convegno

CONTROLLING VIRAL PANDEMICS: A CRUCIAL CHALLENGE FOR HUMANKIND

22 NOVEMBER 2022

A B S T R A C T

Comitato organizzatore: Raffaella CAMPANER (Università di Bologna), Ernesto CARAFOLI (Coordinatore, Linceo, ETH Zurich and University of Padova), Giuseppe IPPOLITO (Ministero della Salute), Gerry MELINO (Linceo, Università di Roma Tor Vergata), Lorenzo MORETTA (Linceo, Ospedale Pediatrico Bambin Gesù), Giorgio PARISI (Linceo, Sapienza Università di Roma), Giuseppe REMUZZI (Istituto Mario Negri, Milano), M. Gabriella SANTORO (Università di Roma Tor Vergata), Roberto SCAZZIERI (Linceo, Università di Bologna)

PROGRAMME

Martedì, 22 novembre

9.00 Roberto ANTONELLI (Presidente dell'Accademia Nazionale dei Lincei): *Welcome and Opening remarks*
Giuseppe IPPOLITO (Ministero della Salute): *Welcome from the Ministry of Health*
Ernesto CARAFOLI (Coordinatore, Linceo, ETH Zurich and University of Padova): *Opening technical remarks*

Chair: **Maurizio BRUNORI** (Linceo, Sapienza Università di Roma)

9.15 Roger KORNBERG (Stanford University, Palo Alto, Nobel Laureate, Chemistry, 1996): *Traditional and innovative Therapeutics for Viral Respiratory Disease*

Chair: **Yang GUANG** (SIAIS, ShanghaiTech University, Shanghai)

9.55 M. Gabriella SANTORO (Università di Roma Tor Vergata): *Viral pandemics: lessons from the past with an eye to the future*

10.35 Zihe RAO (Tsinghua University, Beijing and SIAIS, ShanghaiTech University, Shanghai): *A story of SARS-CoV-2 RNA capping*

11.15 Pausa caffè

Chair: **Wolfgang BAUMEISTER** (Max Planck Institute of Biochemistry, Martinsried)

11.35 Nenad BAN (ETH Zurich): *How coronavirus controls protein synthesis in infected cells*

12.15 Antonio LANZAVECCHIA (National Institute of Molecular Genetics, Milan): *Fighting the viral pandemics:the immunological approach*

12.55 Dario NERI (Philogen, Siena and ETH Zurich): *Fighting and preventing the viral pandemics: construction of a Drug Bank of antiviral compounds*

13.30 Intervallo

Chair: **Roberto SCAZZIERI** (Linceo, Università di Bologna)

14.50 Melissa LEACH (University of Sussex): *Addressing and preparing for viral pandemics – social science approaches*

15.30 Giorgio PARISI (Linceo, Sapienza Università di Roma, Nobel Laureate, Physics, 2021): *Viral pandemics preparedness: the role of science*

Round Table

Lead: **Ernesto CARAFOLI** (Linceo, ETH Zurich and University of Padova)

16.10 Jean Pierre CHANGEUX (College de France and Pasteur Institute, Paris)
Wolfgang BAUMEISTER (Max Planck Institute of Biochemistry, Martinsried)
Yang GUANG (SIAIS, ShanghaiTech University, Shanghai)
Roberto SCAZZIERI (Linceo, Università di Bologna)
Giorgio PALÙ (President of Italian Medicines Agency, AIFA)
Ning MA (Eobiont Biotechnology Co.)
Yun DING (Glaxo Smith Klein [GSK], Boston)
Catherine SMALLWOOD (WHO Europe)

Chair: **Roger KORNBERG** (Stanford University, Palo Alto, Nobel Laureate, Chemistry, 1996)

18.00 Aaron CIECHANOVER (Israel Institute of Technology, Haifa, Nobel Laureate, Chemistry, 2004): *Bioethics and COVID-19, have we forgotten something on the way to cure the disease?*

18.40 Giorgio PARISI (Linceo, Sapienza Università di Roma, Nobel Laureate, Physics, 2021): *Concluding remarks and farewell*

The aim of the Symposium, which is supported by the Academies of Science of the G20 Consortium of National Academies, is to promote a global campaign to fight viral pandemics with innovative means

The Symposium has the patronage of AIFA (Italian Medicines Agency) and has been supported by contributions of Dompè Farmaceutici, Philogen S.p.A., and Eobiont Biotechnology.

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Tutte le informazioni per partecipare al convegno sono disponibili su:
https://www.lincei.it/it/manifestazioni/controlling-viral-pandemics-conference

Nel rispetto delle limitazioni imposte per l'emergenza Covid-19, il numero dei posti in sala sarà limitato (vedi: https://www.lincei.it/it/news/misure-fronteggiare-lemergenza-epidemiologica).
Per partecipare al convegno è necessaria l'iscrizione online
Fino alle ore 10 è possibile l'accesso anche da Lungotevere della Farnesina, 10
I lavori potranno essere seguiti dal pubblico anche in streaming

Traditional and innovative Therapeutics for Viral Respiratory Disease

Roger KORNBERG (Stanford University, Palo Alto, Nobel Laureate, Chemistry, 1996)

Direct acting antivirals are proven therapeutics for viral disease (cf. acyclovir, sofosbuvir). Small molecules for such purposes may be derived in the conventional manner by structure-based drug design. Highly effective anti-SARS Cov2 drug candidates have been developed in this way. The best such molecules, targeting the viral protease, are a million times more potent than Paxlovid, superior in pharmacokinetics, and remarkably, effective against many other viruses (panviral). The problem is that drug development in this way is expensive and time-consuming. Structure-based drug design and preclinical studies take at least three years. The regulatory process for new chemical entities is painfully slow: it takes five years for a safe and effective drug to gain approval by the US FDA. The small molecule approach is clearly unsuited for a future pandemic response.

An innovative approach that overcomes many of the limitations of small molecule drugs involves small interfering RNA (siRNA) and a new delivery platform for nucleic acids and other macromolecules. Whereas siRNA and other large charged molecules fail to enter cells, attachment of a special sterol derivative enables rapid efficient penetration. An siRNA with the nucleotide sequence of a conserved SARS CoV2 protein effects a 99.9% reduction in viral load in infected cells. The siRNA is both prophylactic and therapeutic. It can be formulated as a dry powder, stable indefinitely under ambient conditions. Response to a future pandemic strain will be immediate, because the nucleotide sequence can be changed to that of the new strain and the siRNA produced on a synthesizer. The FDA may approve a change in sequence without delay.

Viral pandemics: lessons from the past with an eye to the future

M. Gabriella SANTORO (Università di Roma Tor Vergata)

Viral infections have accompanied the rise of human civilization causing profound loss of life and leaving a lasting imprint on human history. From the devastating Smallpox virus in ancient Egypt, to the 20th century, punctuated by lethal viral epidemics and pandemics such as the Spanish Flu, HIV, Ebola, SARS and MERS, new emerging viruses continue to pose a major threat to human health. Nowadays, despite the intense work of national and international health agencies, the SARS-CoV-2 coronavirus took us by surprise and caught the world unprepared. Notably, recent emerging infections have been caused by single-stranded RNA viruses: indeed rapid replication of RNA genomes, combined with low-fidelity RNA polymerases, provide the basis for an endless source of new emerging viruses, also expanding probabilities for zoonosis. Whereas preventive measures by vaccination have been successful in protecting humanity from many viral diseases such as smallpox and polio, the vast majority of viral infections still have no vaccine or treatment options. In addition to crucial vaccine development, novel antiviral therapeutic strategies are urgently needed. With few exceptions, therapeutic approaches to combat viral infections have traditionally focused on targeting unique viral components or enzymes. However, since future pathogens with pandemic potential cannot be predicted, also broad-spectrum antiviral drugs should be developed for immediate response, and to circumvent rapid emergence of drug-resistant viruses. Targeting host factors that are essential for the virus life cycle, rather than pathogen components directly, has received increasing attention and has recently become possible due to major advances in the comprehension of the molecular basis of virus/host interactions. In addition to traditional antiviral chemotherapy, this strategy opens new perspectives in the fight against future pandemics.

A story of SARS-CoV-2 RNA capping

Zihe RAO (Tsinghua University, Beijing and SIAIS, ShanghaiTech University, Shanghai)

The coronavirus family has many pathogens that cause severe human diseases, including SARS, MERS and COVID-19. Till October 2022, COVID-19 has caused over 600 million infections and more than 6.5 million deaths.

Starting from the SARS outbreak in 2003, our group has been dedicated to understanding coronavirus Replication-Transcription Complexes (RTCs). During the early part of the COVID-19 outbreak, we rapidly initiated a structural study of SARS-CoV-2 RTCs, aiming to dissect the key mechanisms for SARS-CoV-2 in human cells and provide structural information to discover potent antivirals. With great efforts from our laboratory and outside collaborations, we successfully determined the structure of the central RTC (C-RTC) composed by nsp12 (RNA-dependent RNA polymerase, RdRp) with cofactors nsp7 and nsp81, providing the first picture to visualize this key antiviral target. We also elucidated the mechanism of C-RTC catalysis and how remdesivir (RDV) inhibits the synthesis of RNA. This was achieved by determining the structure of C-RTC in complex with the template-product duplex RNA and the active form of RDV2. Subsequently, we presented the structure of the elongation RTC (E-RTC), showing how nsp13 (helicase) unwinds the highly-ordered structure in genome to yield the functional template for RNA synthesis in C-RTC3. After that, we discovered a key intermediate state of RTC leading towards mRNA capping [Cap(-1)'-RTC], demonstrating the nsp12 NiRAN is indeed the key enzyme to catalyze the second capping action and how it presents nsp9 as an "adaptor" for the further recruitment of capping enzymes into RTC4. In a following study, we assembled Cap(0)-RTC by Cap(-1)'-RTC and nsp10/nsp14, showing how the co-transcriptional capping and an in trans backtracking mechanism for proofreading concert in one RTC5. In our most recent work, we discovered a previously unknown protein modification - RNAylation on nsp9, and demonstrated nsp12 NiRAN utilizes the RNAylated nsp9 and GTP as substrates to synthesize the GpppA cap core, reasoning a novel RNA capping pathway6. We also showed that the nucleotide analogue inhibitors (NAIs) can be linked to nsp9 by NiRAN and thus block the occurrence of RNAylation and GpppA formation, furthering the understanding of the mechanism of action of NAIs. An 'induce-and-lock' mechanism is proposed to design new inhibitors against SARS-CoV-2 RNA capping. These works not only provides a basis to understand SARS-CoV-2 proliferates in the host cells through a structural biology lens, but also sheds new light for antiviral development against rapidly emerging SARS-CoV-2 variants.

1 Gao, Y. et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. Science 368, 779-782, doi:10.1126/science.abb7498 (2020).

2 Wang, Q. et al. Structural Basis for RNA Replication by the SARS-CoV-2 Polymerase. Cell 182, 417-428.e413, doi:10.1016/j.cell.2020.05.034 (2020).

3 Yan, L. et al. Architecture of a SARS-CoV-2 mini replication and transcription complex. Nat Commun 11, 5874, doi:10.1038/s41467-020-19770-1 (2020).

4 Yan, L. et al. Cryo-EM Structure of an Extended SARS-CoV-2 Replication and Transcription Complex Reveals an Intermediate State in Cap Synthesis. Cell 184, 184-193 e110, doi:10.1016/j.cell.2020.11.016 (2021).

5 Yan, L. et al. Coupling of N7-methyltransferase and 3'-5' exoribonuclease with SARS-CoV-2 polymerase reveals mechanisms for capping and proofreading. Cell 184, 3474-3485 e3411, doi:10.1016/j.cell.2021.05.033 (2021).

6 Yan, L. et al. A mechanism for SARS-CoV-2 RNA capping and its inhibition by nucleotide analogue inhibitors. Cell, doi:10.1016/j.cell.2022.09.037 (2022).

How coronavirus controls protein synthesis in infected cells

Nenad BAN (ETH Zurich)

Our group is investigating bacterial and eukaryotic ribosomes and their functional complexes to obtain insights into the process of protein synthesis. Building on our studies aimed at revealing the structures of eukaryotic cytosolic ribosomes, we are now investigating eukaryotic translation initiation, regulation of protein synthesis, and how viruses reprogram host translation. Previously, we studied how Hepatitis C virus genomic RNA can bind mammalian ribosomes to achieve translation of viral mRNAs in the absence of several canonical cellular translation initiation factors. With our recent research activities we contributed to the understanding of how SARS-CoV-2, the virus that is responsible for the COVID-19 pandemic, shuts off host translation to prevent cellular defence mechanisms against the virus (Schubert et al. 2020). Furthermore, using a combination of cryo-electron microsocpy and biochemical assays we also investigated the mechanism of programmed ribosomal frameshifting, one of the key events during translation of the SARS-CoV-2 RNA genome that leads to synthesis of the viral RNA-dependent RNA polymerase and downstream viral proteins (Bhat et al. 2021).

Schubert K, Karousis ED, Jomaa A, Scaiola A, Echeverria B, Gurzeler LA, Leibundgut M, Thiel V, Mühlemann O, Ban N. (2020) SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. Nat Struct Mol Biol. (10):959-966

Bhatt PR, Scaiola A, Loughran G, Leibundgut M, Kratzel A, Meurs R, Dreos R, O'Connor KM, McMillan A, Bode JW, Thiel V, Gatfield D, Atkins JF, Ban N. (2021) Structural basis of ribosomal frameshifting during translation of the SARS-CoV-2 RNA genome. Science. 372(6548):1306-1313.

Fighting the viral pandemics:the immunological approach

Antonio LANZAVECCHIA (National Institute of Molecular Genetics, Milan):

In the last 3 years the scientific community has been engaged in an extraordinary effort to fight the SARS-CoV-2 pandemic. Fundamental advances in coronavirus biology, in vaccine design and in the isolation of human monoclonal antibodies were made in the last two decades have contributed to a rapid and successful response. I will review the immunological approach to COVID-19 that is based on the development of effective vaccines and therapeutic monoclonal antibodies. I will highlight the importance of human studies to define the role of innate immunity, of specific T cell and antibody responses and of immunological memory. I will also suggest that we need to critically reconsider how to define the correlates of protection that are used to evaluate the efficacy of vaccines and antibodies at face of immune escape variants

Fighting and preventing the viral pandemics: construction of a Drug Bank of antiviral compounds

Dario NERI (Philogen, Siena and ETH Zurich)

The recent experience in the fight against COVID-19 has shown that, in addition to vaccines and monoclonal antibodies, small organic drugs may play an important role in the fight against the disease.
Virtually every drug is, to begin with, a protein binder. The discovery of protein ligands is crucially important for the development of new efficacious drugs. Traditionally, the discovery and development of small organic drugs is a lengthy and expensive process, which is hardly compatible with the timelines imposed by a pandemic emergency.

However, recent break-through innovations in the field of drug discovery dramatically accelerate the identification of pharmaceutical agents, which may have the required potency and specificity. In particular, DNA-encoded chemical libraries (DELs) are ideally suited for the discovery of protein binders [1]. DELs are collections of organic compounds, individually attached to distinctive DNA fragments, that serve as amplifiable identification barcodes.
DEL technology allows the construction and screening of compound libraries of unprecedented size and quality, thus facilitating the identification and validation of protein ligands.
In this lecture, I will present recent results on the use of DEL technology for the rapid identification of protein binders and for their translation to clinical trials. I will also show how encoded libraries can be used to fight COVID-19 and propose a possible avenue for the use of DEL technology in the preparation against future pandemics.
References:
[1] Neri & Lerner (2018) Annu. Rev. Biochem., 87, 479

Addressing and preparing for viral pandemics – social science approaches

Melissa LEACH (University of Sussex)

Recent viral epidemics and pandemics – from Ebola and Covid-19 to Monkeypox and more – have underlined the importance of social science approaches in both preparedness and response. This presentation will draw on the findings of several recent research programmes – including a Wellcome Trust funded Collaborative Award on Pandemic Preparedness: Local and Global Concepts in Tackling Disease Threats in Africa; the Social Science in Humanitarian Action Platform, and the Covid Collective, to outline key insights and lessons. First, social science analysis highlights the range and extent of pandemic impacts. These extend beyond direct impacts of viral disease on human health, to include indirect health impacts on a wide range of physical and mental conditions as availability and access to health services are challenged. They also include impacts of public health and control measures on economies, food, livelihoods, social cohesion and citizen-state relations. Negative impacts are often felt most seriously where people are already vulnerable, adding to intersecting precarities and forms of deprivation. In these ways social science approaches underline why effective pandemic prevention and control is so important. Second, social science analysis is critical to designing and implementing effective control measures. Where these involve pharmaceuticals, social sciences provide crucial insights into how these might be understood and received by populations; what anxieties might arise around vaccines and treatments; how these might unfold in different social and political contexts, and how to mitigate these. Social sciences also underline the complementary value of non-pharmaceutical measures aimed at controlling transmission, the kinds of behaviour change these require, and the social considerations needed for these to be effective. In particular, recent epidemics have highlighted the importance of community engagement and of communication approaches that build sensitively on local understandings and priorities. Third, insights from social sciences highlight a range of capacity issues – with staff and training, resource availability, and equitable, effective systems and technologies – needed to ensure that surveillance and control measures operate effectively. And fourth, social science approaches, in interdisciplinary combination with other sciences, are vital in understanding the conditions in which viral outbreaks emerge and and outbreaks grow into pandemics. These include changes in human-animal-environment relations that lead to zoonotic spillover, and their wider political-economic drivers; changes in human vulnerability and immunity, shaped by wider inequalities, and patterns of settlement, mobility and vulnerability that create conditions for rapid disease spread. Overall, the presentation will argue for a wider set of approaches to pandemic preparedness that include but go beyond drugs and vaccines; address the

wider social, economic and political contexts in which disease develops and control is enacted, and that recognise and connect preparedness efforts from local, national and global settings. This in turn requires approaches that are interdisciplinary – integrating diverse social and natural sciences – and transdisciplinary, engaging with policymakers, practitioners and citizens themselves.

Viral pandemics preparedness: the role of science

Giorgio PARISI (Linceo, Sapienza Università di Roma, Nobel Laureate, Physics, 2021)

Each year there are the annual governmental meetings of the G7 and of G20. Before these meetings there are Academic meetings, the S7 Academic meeting and the S20 (and sometimes the SSH7 and SSH20).
Starting from the S20 meeting in Rome, there have been documents signed by the Academies that discuss problems related to pandemies.
I will illustrate them and summarize the recommendations.
The documents are
https://www.lincei.it/sites/default/files/documenti/Relazioni_Int/2021_S20_Joint_Statement_Pandemic.pdf
https://www.lincei.it/sites/default/files/documenti/Relazioni_Int/2021_S7_Statement_Data.pdf
https://www.lincei.it/sites/default/files/documenti/Relazioni_Int/One-Health_S7_2022_final_web.pdf
https://www.lincei.it/sites/default/files/documenti/Relazioni_Int/Antivirals_S7_2022_final_web.pdf
https://www.lincei.it/sites/default/files/documenti/Relazioni_Int/2022_S20_COMMUNIQUE_FINAL_22sept2022.pdf

Tavola rotonda

Jean Pierre CHANGEUX (College de France and Pasteur Institute, Paris)

Classically, the field of drug therapy relied upon “the relationship betwen isosterism & competitive phenomena”. The new strategy proposed for drug design in neuropharmacology is based upon the concept of allosteric interaction initially proposed to account for the inhibitory feedback mechanism mediated by bacterial regulatory enzymes. In contrast with the classical mechanism of competitive, steric, interaction between ligands for a common site, allosteric interactions take place between topographically distinct sites and are mediated by a discrete & reversible conformational change of the protein.
The concept was soon extended to membrane receptors for neurotransmitters and shown to apply to the signal transduction process which, in the case of the nicotinic receptor for acetylcholine (nAChR), links the ACh binding site to the ion channel. Pharmacological effectors, referred to as allosteric modulators, such as Ca++ ions or ivermectin, were discovered that enhance the transduction process when they bind to sites distinct from the orthosteric ACh site and the ion channel. The recent X-ray structures, at atomic resolution, of the resting & active conformations of prokaryotic homologs of the nAChR and eukaryotic receptors including the nAChR itself, in combination with atomistic molecular dynamics simulations reveal several distinct quaternary transitions in the transduction process with tertiary changes which profoundly modify the boundaries between subunits. These interfaces host orthosteric and allosteric modulatory sites which structural organization changes in the course of the transition. The model emerging from these studies has lead to the conception and development of several new pharmacological agents.
Such allosteric transitions mediate the modulation of brain circuits involved for instance in the dual action of nicotine both as a drug of abuse and as a cognitive enhancer. By capitalizing on the constantly developing structural information at high resolution, the aim is the design of orthosteric and allosteric modulators for ligand gated ion channels

which are not only selective but also specific to their site on one conformation of the receptor over the others. The strategy has been termed state-based pharmacology which should lead to the rational design of pharmacological agents with a characteristic physiological action such as activators vs inhibitors vs desensitizers.
Some of them might be relevant to the design of anti-COVID-19 drugs.
Following the hypothesis that nAChRs may play a role in the pathophysiology of Covid-19 infection, ivermectin a positive allosteric modulator of a7nAChRs, was found, in SARS-CoV-2- infected hamsters, to prevent clinical deterioration, reduce olfactory deficit, and limit the inflammation of the upper and lower respiratory tracts. The effects of IVM are currently under study.
These developments pave the way to a new orientation of neuropharmacology.

Roberto SCAZZIERI (Linceo, Università di Bologna)

Preparedness, and resilience to shocks resulting from it, are multi-dimensional concepts. This conference addresses the multi-dimensional character of viral pandemic preparedness from a science-based interdisciplinary perspective. Its main focus is on the immunological and pharmaceutical dimensions while acknowledging that pandemic preparedness reaches deeply into the socio-cultural, economic, and political domains. A common conceptual framework underlying the conference is the emphasis on the intrinsic uncertainties associated with pandemic outbreaks, the variety of complementary measures aimed at pandemic control, and the call for flexibility as means of responding to shocks whose likelihood may be known but whose specific features are highly uncertain and unpredictable.
Future pandemic outbreaks are likely but their specific features are uncertain. This combination of likelihood and uncertainty provides a guideline to effective preparedness measures. Uncertainty itself is multi-dimensional, and there is an established distinction between uncertainty as calculable risk, (risk evaluated in terms of a given probability distribution of events), uncertainty stricto sensu, in which events are known but not their probabilities, and fundamental uncertainty, in which not even the events that may or may not happen are known (this is the case of the so-called 'unknown unknowns'). Professor Melissa Leach has added to the above dimensions of uncertainty the dimension of ambiguity, which may result from contested visualizations of pandemic outbreaks and their dynamics across different individuals or social groups.
Pandemic outbreaks may share to different degrees all the above dimensions of uncertainty. This brings to light the need of flexibility as prerequisite for effective preparedness. Pandemics are processes at the interface between the biological and the socio-economic domains. This calls for a flexible response mechanism based on the availability of a broad spectrum of immunological, pharmaceutical, socio-cultural and economic measures, which could be implemented in different combinations depending on the specific features of each pandemic outbreak. The most important condition for the context-relevance and effectiveness of controlling measures under uncertainty is deeper understanding of the biological, social, and economic structures uinderlying the dynamics of pandemic outbreaks. Deeper structural knowledge is an essential prerequisite both for the understanding of fundamental (relatively invariant) structures and for the identification of the variety of forms that those structures may take under different conditions. This type of structural understanding has far-reaching implications beyond the biological domains due to the manifold interdependencies between biological, anthropological, and socio-economic structures, In this connection, interdisciplinary reaseach is of fundamental importance. Pandemic preparedness presupposes deeper understanding of the structures of life in their manifold dimensions, with due attention paid to the distinction between fundamental structures and the variety of their workings

in different contexts. This distinction is central to the identification of flexible preparedness programmes under conditions of uncertainty.

Bioethics and COVID-19, have we forgotten something on the way to cure the disease?

Aaron CIECHANOVER (Israel Institute of Technology, Haifa, Nobel Laureate, Chemistry, 2004)

While rushing to develop a vaccine to the COVID-19 Pandemic and to take care of the mass of sick patients, many bioethical issues have been piled up that will need careful attention as part of the preparedness for the next Pandemic that will certainly come. Among them are: (i) how to prioritize treatment of those who need respiratory assistance; (ii) can we neglect other important issues- climate change, for example - giving priority for handling the Pandemic; (iii) Vaccine hesitancy – its sources and how to handle it; (iv) the Pandemic of Infodemics and its huge damage; (v) the rise of racism. Some of these problems are related to the bioethical issues we confront while ushering in the era of Personalized Medicine like the very basic definition of the pillars of 'canonical' medicine – the patient, the disease and the treatment that will certainly need re-definition