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Conceptual and Methodological Aspects of Biomedical Research

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INVITED TALKS

Lucie Laplane (CNRS, IHPST Université Paris I-Panthéon-Sorbonne, Institut de Cancérologie Gustave Roussy)

Stem cell: Between philosophy and biology

Stem cells play a critical role in the development, daily renewal, and reparation/regeneration of tissues. They are also involved in various diseases in particular cancers. Yet, there is a lot that remains to be understood about them and the traditional view is being increasingly debated. This is both a biological and a philosophical issue. Mixing both approaches, I will discuss the following questions: (1) What kind of property is stemness? I will show that stemness can be four types of properties depending on tissues and contexts (2) Does it matter? I will highlight practical consequences of each type of stemness for cancer treatment (3) Is stemness stable? I will review empirical data questioning stemness stability and suggesting that some cancers could be associated with a switch in stemness property. (4) Is stem cell a unified biological category? I will end with a perspective on how to handle the debate on stemness natural kind by mixing philosophy, experimental biology and phylogenetic analyses.

Barbara Osimani (Faculty of Medicine, Polytechnic University of Marche at Ancona)

The Causal Structure of Epistemic Environments

According to the Variety of Evidence Thesis (VET), items of evidence from independent lines of investigation are more confirmatory, *ceteris paribus*, than e.g. replications of analogous studies. Although intuitively plausible, this thesis is known to fail (Bovens and Hartmann 2003, Claveau 2013, Osimani and Landes 2020). We investigated the epistemic dynamics of VET failure by changing the model parameters regarding source "reliability". The comparison of our results with previous attempts to analyse the VET illustrates how distinctive ways in which (un)reliability may be modelled (and thought of), impact on the inferential import of consistent results (see also Wheeler 2009, Wheeler and Scheines 2013).
The analysis of such structural relations between items of evidence, the investigated hypothesis, and hypotheses regarding the evidence source itself promises to be an essential step forward in understanding (scientific) reasoning and in shaping scientific methodology (Osimani2020).

Anya Plutynski (Department of Philosophy, Washington University in St. Louis)

Big Data, AI, and Precision Oncology: Is More Better?

The hope of precision oncology is that identification of specific molecular markers will enable better risk stratification of cancers of specific types and subtypes, more fine-grained prognoses, and targeted treatments, with fewer side effects (Collins and Barker, 2007). While surgery, chemotherapy and radiation are effective against many cancers, they have lasting health consequences, toxic side effects, and may fail patients with advanced disease. Drawing upon recent dramatic recent successes in immune therapy, as well as earlier "breakthrough" treatments, such as the kinase inhibitors (imatinib, gefitinib), many are hopeful for the future development and extension of precision therapy (Hyman, et. al., 2017.) There are, however, vastly different views about the current status and future promise of precision oncology. Optimists, such as Collins and Varmus suggest that: "Oncology is the clear choice for enhancing the near-term impact of precision medicine." (Collins and Varmus, 2015, 793). Critics contend that there are relatively few cancer patients likely to benefit, lack of evidence of lasting benefit (frequent recurrence and relapse), improperly validated biomarkers, high levels of toxicity, and the costs of drugs are prohibitive (Tannock, et. al, 2016; Prasad, et. al., 2016; Ioannids, 201; Chin-Yee, et. al., 2019; Hey, et. al., 2016, 2020) To be sure, there are several challenges facing precision oncology – some due to the nature of cancer itself, and some due to practical and methodological challenges facing design of trials, coordination of researchers, and translation to the clinic. Designing trials and treatments that overcome all of these practical challenges is, needless to say, enormously difficult. Some have suggested that AI will come to the rescue.

With large genetic databases linked to patient relevant data, perhaps artificially intelligent learning systems could organize this information and provide clinicians with better, smarter diagnostic and treatment protocols? This talk will consider several methodological, practical, and ethical challenges facing this proposal. These challenges span the spectrum from concerns about the input (quality and quantity of samples in service of disease and gene classification), to data harmonization (e.g., cooperation on agreed nomenclature and operational measures of biomarkers), to linking genomic data with therapeutic data on effective intervention (while also protecting privacy), to enabling clinicians and patients to use and trust AI in medical decision making. I argue that these hurdles are far more serious than has perhaps been anticipated in the rush to promote big data in precision oncology.

Jaromir Sramek (Institute of Histology and Embryology, First Faculty of Medicine, Charles University in Prague & Czech Skeptics' Club Sisyfos)

Evidence-based medicine: Fisher, Bayes, and medical education in the Czech Republic

From the physician's point of view, the evidence-based medicine is a tool supporting clinical decision based on the formal analysis of previously published evidence. There are two main approaches to summarize the evidence, the Fisherian or frequentist one and the Bayesian one. Both approaches have not only advantages but also disadvantages and, thus, understanding of the principle is essential for successful facing the pitfalls.
Unfortunately, medical education in the Czech Republic is relatively conservative, evidence-based medicine has not yet found a proper site in the curriculum. For this reason, some misconceptions springing from unrecognized pitfalls of the evidence-based medicine are common among physicians. Although bizarre misconceptions like *"I have some study telling it, therefore I'm right"* are probably rare, some physicians may fall into troubles outside the comfort zone bordered by the strong meta-analyses and evidence-based clinical guidelines.
I will show examples of common misconceptions of different severity. Obvious pathological examples will be from the archive of the Czech Skeptics' Club Sisyfos, milder examples will be based on the questionnaire sent to young doctors. As other tools, also the evidence-based medicine can be useful only if it is used properly. Improper use can be harmful for patients, therefore attention should be paid also to the insight-based education of physicians.

Jacob Stegenga (Department of History and Philosophy of Science, University of Cambridge)

The Medicalisation of Sexual Desire

Medicalisation is a social phenomenon in which conditions that were once under legal, religious, personal or other jurisdictions are brought into the domain of medical authority. Low sexual desire in females has been medicalised, pathologised as a disease, and intervened upon with a range of pharmaceuticals. There are two polarised positions on the medicalisation of low female sexual desire: I call these the mainstream view and the critical view. I assess the central arguments for both positions. Dividing the two positions are opposing models of the aetiology of low female sexual desire. I conclude by suggesting that the balance of arguments supports a modest defence of the critical view regarding the medicalisation of low female sexual desire.

Meritxell Alberich-Jorda (Laboratory of Haematooncology, Institute of Molecular Genetics, Czech Academy of Sciences)

Understanding the molecular basis of blood cell production: the b-catenin-TCF/LEF signaling pathway in hematopoiesis

Hematopoietic stem cells and progenitors, collectively known as HSPCs, sustain mature blood cell production throughout the lifetime of an organism. HSPCs respond to stress conditions, such as infections, by tailoring a response adequate to resolve the insult. Thus, identifying the mechanisms that regulate HSPC function in homeostasis and stress situations is important for understanding the dynamic nature of the system. One of the critical yet controversial pathways in HSPC regulation is the canonical Wnt signaling pathway. This pathway is mediated by interaction of b-catenin with the TCF/LEF transcription factors and subsequent transcription of Wnt-

target genes. To clarify the role of the b-catenin-TCF/LEF transcription complex in HSPC during normal and stress conditions, we generated a mouse model expressing a truncated dominant negative form of the human TCF4 transcription factor (dnTCF4) which specifically abrogates b-catenin-TCF/LEF interaction. Disruption of the b-catenin-TCF/LEF interaction resulted in the accumulation of HSPCs and reduced neutrophilic differentiation. Inhibition of b-catenin signaling compromised activation of the emergency granulopoiesis program, which requires maintenance and expansion of HSPCs during infection. Consequently, dnTCF4 mice were more susceptible to succumb to infection. Importantly, genetic and chemical inhibition of b-catenin-TCF/LEF signaling in human primary cells reduced neutrophilic differentiation, whereas its activation enhanced differentiation. Altogether, our data indicate that the b-catenin-TCF/LEF complex controls proper differentiation of HSPCs into neutrophils in steady-state and emergency conditions, opening venues for clinical intervention that require enhanced or reduced production of neutrophils.

Sona Hubackova (Laboratory of Molecular Therapy, Institute of Biotechnology, Czech Academy of Sciences)

Targeting cellular senescence as a new strategy in treatment of age-related diseases.

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Cellular senescence is a form of cell cycle arrest that limits the proliferative potential of cells, which represents barrier against tumorigenesis. However, inability of immune cells to subsequently eliminate senescent cells from the organism may lead to inflammation, carcinogenesis or development of age-related diseases like type 2 diabetes mellitus (T2DM), which represents a major health problem with increasing prevalence of the pathology. Despite extensive knowledge, current therapies have limited efficacy, prompting a search for novel therapeutic options.
Senescent cells remain metabolically active. Increased oxygen consumption, energy production, lipid catabolism and levels of ROS due to hyperactive mitochondrial respiration indicate a robust metabolic shift and show importance of mitochondria in maintenance of senescence. Since mitochondria act as a key player in promoting and establishing growth arrest, their targeting represent a new strategy for the treatment of age-related diseases and senescence-associated pathologies.
Searching for pharmacological elimination of senescent cells, we developed a new promising senolytic agent MitoTam (mitochondrially-targeted tamoxifen). We found, that MitoTam treatment markedly improves glucose control and decreases body weight in mice with diet-induced obesity and T2DM. These improvements are associated with a reduction in the number of lipid-accumulating senescent cells in the organism and rejuvenation of the adipose tissue. All these data indicate that MitoTam may be a novel approach to the treatment of obesity and T2DM, and related complications.

Michal Smahel (Laboratory of Immunotherapy, Faculty of Science, Charles University in Prague & BIOCEV)

Cancer Immunotherapy: Overcoming Tumor Immune Escape

Cancer immunotherapy is increasingly utilized in clinical practice, as numerous clinical trials showed its benefit in patients with advanced tumors resistant to other types of therapy, particularly after treatment with monoclonal antibodies targeting immune checkpoints. However, despite this breakthrough in cancer therapy, the efficacy of checkpoint blockade is limited and most patients are still resistant to this treatment. During tumor development, oncogenic cells are under the selection pressure of the host immune system. Due to their genetic instability, which leads to high mutation rate and epigenetic modifications of gene expression, tumor cells can acquire adaptations that provide them with a survival advantage and enable their evasion of immune reactions. The downregulation of surface expression of major histocompatibility complex class I molecules is a frequent mechanism of immune

escape in various human malignancies. In patients treated with immune checkpoint inhibitors, genetic analyses proposed an association between treatment failure and impairment of interferon gamma signaling. In our studies, we develop mouse tumor models, that correspond to immune escape mechanisms found in human cancers, and strive to enhance cancer immunotherapy to overcome these escape mechanisms.

Jiri Vejmelka (Department of Internal Medicine, Thomayer Hospital & Third Faculty of Medicine, Charles University in Prague)

Gut microbiota modulation in IBS – novel challenges

Jirí Vejmelka and Pavel Kohout

Our clinical practice and research are focussed on human microbiota and beneficial approaches to harmonize gut microbiota diversity and function. Human microbiota plays essential role in holobiont concept and is considered to be unique and integrating organ. We provide both pre-, pro- and synbiotics counselling associated with clinical nutrition support and general internal medicine and also fecal microbiota transplantation in patients with severe gut microbiota dysbiosis. Our current clinical trial is focussed on fecal microbiota transplantation impact in patients suffering from irritable bowel syndrome. Donors are recruited from medical students and regular blood donors. Fecal microbiota transplantation and other microbiota-based therapies represent progressive preventive and treatment tool that can maintain and restore gut microbiota and ensure human body homeostasis. Stool banking and complex microbiota donation have become very interesting phenomenon nowadays. Sharing human microbiota helps to protect our human organisms and to fight against severe dysbiosis as well as against multidrug resistant bacteria. Sharing our clinical experience, networking and efficient human microbiota - associated data analysis and especially human microbiota welfare promotion should be highlighted to avoid global dysbiosis.

CONTRIBUTED PAPERS

Alessandro Blasimme (Department of Health Sciences and Technology, ETH Zurich)

Interpreting medical algorithms: Opacity, explainability and the epistemology of future medicine

Machine learning (ML) is a form of artificial intelligence holding promise to partially or fully automate important medical acts: from triage to diagnosis, and from prognosis to treatment. Intense scholarly discussion is underway regarding specific epistemological issues in this field, namely, the problems of ML opacity and explainability. ML algorithms autonomously uncover statistically relevant correlations in training datasets and then apply such self-learnt regularities to new input data. In other words, it is not the programmer that decides which rules the algorithms should follow in its operations. It is the algorithm itself that, based on autonomously learnt rules, accomplishes a given task, such as a diagnostic assessment. The rules the ML algorithm has learn are unknown to both programmers and users, who therefore remain agnostic regarding underlying causal relations between input and output variables. Because of their purely associative nature, ML algorithms are said to be atheoretical, and they are often depicted metaphorically as opaque, non-transparent, or as black boxes.

Many argue that such algorithms warrant clinical use only if they can be made explainable, while others maintain that the accuracy of such systems is sufficient to justify their use, despite their opacity. I will show that both positions are mistaken and advance a third one. More specifically, I set out to clarify what opacity and explainabilty mean, and discuss whether causally agnostic ML algorithms are at odds with epistemically justified medical acts. My thesis is that opaque ML algorithms do not undermine justification, provided one can control for overfitting and biases in training datasets, and that such epistemic precautions require some form of causal knowledge to be adopted.

In section one, I will provide a brief overview of the use of ML in medicine. Section two offers a conceptual analysis of opacity. To this aim, I will distinguish between *algorithmic opacity* (the fact that one cannot access the rules learnt by the algorithm) and *epistemic opacity* (the fact that such algorithms do not offer mechanistic insight into the underlying causal relations between input and output variables).

In section three, I analyze explainability in relation to both algorithmic and epistemic opacity, and argue that while ML algorithms cannot be expected to be neither explainable nor explanatory, they are not entirely atheoretical either as they both depend on and can foster causal explanations of medical phenomena. In other words, opaque algorithms do not prevent causal interpretation, that is, a necessary (albeit not sufficient) condition for any justified medical decision.

In the fourth and last section, I critically discuss frequently entertained arguments according to which the opacity of ML algorithms is offset by their empirical accuracy. In particular, my critique of such arguments attacks their major premise, that is, the claim that, in medicine, statistical association is epistemically superior to causal inference. I conclude with some further thoughts on the epistemic implications of opacity.

Marina DiMarco (Department of History and Philosophy of Science, University of Pittsburgh)

Wishful Intelligibility

Epidemiological explanation often has a \black box" character, meaning the intermediate steps between some putative cause and effect of interest are unknown. Black boxes are particularly common in this domain because ethical constraints on inquiry prevent epidemiologists from manipulating many causal variables of interest in human populations, such that epidemiological causal inference is often probabilistic or statistical, in contrast to more paradigmatically \experimental" inquiry. Consequently, the black boxes of epidemiological explanation have been variously described as mere predictive heuristics; as obstacles, or even threats to scientific understanding. Philosophers and epidemiologists alike have argued that specifying intermediate causes to fill in black boxes improves causal explanations by making them intelligible, and better targets for public health intervention. Specifying the links between the ends of a causal chain is supposed to confer certainty, understanding, and reasons to expect a causal relationship to be stable or invariant across populations of interest.
I propose to address an important aspect of the relationship between black box explanations and scientific understanding in epidemiology. I argue that adding information about intermediate causes can be an unreliable guide to improving epidemiological explanation because it may introduce additional uncertainty about causal inference and may convey a false sense of understanding. Using Woodward's (2010) notion of the stability of biological causes, I show that specifying intermediate causes can mislead us about the stability of a causal relationship. I diagnose this as an instance of a more general problem that I call wishful intelligibility, which occurs when scientists misjudge the limits of the pragmatic intelligibility conferred by certain features of an explanation. To illustrate this, I consider an example of epidemiological explanation involving the social determinants of health. My argument offers a new reason to prefer black box explanations in some contexts: not despite, but because of, their lack of information about intermediate causes. This preference is compatible with non-factive accounts of scientific understanding, and has the consequence that filling in black boxes is not a necessary source of pragmatic intelligibility, but a contingent one.

Christopher Donohue (National Human Genome Research Institute, NIH)

'Missing Heritability' and the 'Existential' Crisis of Genomics

The International HapMap Project, developed by the National Human Genome Institute in the early 2000s, to power GWA (genome wide association) studies so as to make robust associations (if not causal inferences in some cases) between human variation and disease phenotype. However, GWAS has not identified the expected variations nor elucidated genomic disease architecture to the extent predicted, especially for common, complex diseases. This is the problem of 'missing heritability.' Thus, this problem leaves open the possibility that many common diseases are due to mostly environment and exposure rather than the influence of a putative, causal variant

or assemblage of variants; or conversely, the variants are too difficult to identify. I underscore how this is related to the initial emphasis of the HapMap on common SNPs (due to technology limitations and experience from the Human Genome Project), which lead to a simplified view of genome biology. The delay in defining structural and rare variation (part of an emerging 'ecology of variation') has also led to conceptual difficulties in recent genomic medicine, including complexities with reference genomes and variant calling in genomic medicine.
I argue, as it stands now, the initial hypothesis of the HapMap, common disease, common variant (CDCV) may no longer be viewed as tenable. Furthermore, as the HapMap developed into1000 Genomes program by 2008, the notion of a "comprehensive" catalogue of variation and in particular rare variation, was quite distinctive and different from the 'commonality' hypothesis which motivated the original HapMap.
This betrays in a certain sense some of the major assumptions of the Human Genome Project (HGP) itself. The HGP was prefaced on the assertion that a single sequence would revolutionize medicine and that what was most important were the common features genome biology, as a shared medical inheritance for humanity. The simplicity and the elegance of the genome project, however, has given way to the realities of complexity: types of variation (rare and common) and the continual difficulties integrating structural variation into genomic resources, in particular the Genome Reference.
I end with the discussion that if common disease is not in fact primarily genomic, then genomics as a method will have not born out the promises of the Human Genome Project. As importantly. I also contend that many issues might be addressed with this issue if scientists develop a fuller notion of 'heritability', pointing out that many statisticians, for example Augustine Kong, are in the beginning stages of doing just this. Last, I end with whether a possible solution to the 'missing heritability' issue is rather thinking of common disease phenotype not as a sum of hereditary elements plus environmental influences, but an 'emergent' quality which comes through an interaction of both, but not reducible to both.

Michaela Egli (Department of Philosophy, University of Geneva)

Can Pragmatic Clinical Trials Measure Effectiveness?

Clinical researchers increasingly use so-called 'pragmatic' trial designs (pRCTs) for testing the benefit and safety of drugs. Combining the methodological rigour of ideal randomized controlled trials (RCTs) with clinically relevant questions and settings, researchers claim that pRCTs provide directly applicable results to questions from clinical practice. If this assumption is correct, pragmatic trials could provide a solution to 'the problem of extrapolation', or 'the problem of external validity' – at least for clinical research.
Unlike RCTs, pragmatic trials include diverse subpopulations in the study – e.g., the elderly or patients with comorbidities – and dispense with many constraints about treatment decisions, physicians' expertise or patients' adherence to treatments. The driving objective is to interfere as little as possible with routine clinical practice and to answer questions that are directly relevant to physicians, patients or policy makers. Most importantly, pragmatic trials are widely held to provide direct evidence of *effectiveness* of medical treatments, i.e., the benefit of a drug for real patients in daily clinical practice. Such evidence is urgently needed, since ideal RCTs are known to have very limited applicability beyond the context of the study, i.e., they lack 'external validity'. A closely related discussion in the philosophy of science is 'the problem of extrapolation'. Philosophers aim to find strategies to infer a conclusion about a target population from knowledge about a study population. This includes but is not limited to inferring the effectiveness of drugs for real patients based on their effects in randomized controlled trials.
In my contribution to the discussion, I critically examine the assumption that pRCTs solve the problem of extrapolation. To this end, I first clarify what the problem of extrapolation is about and distinguish it from the question of external validity. Although the labels are sometimes used interchangeably, I maintain that external validity says something *about the study*, i.e., it assesses whether a certain study is a good model for a specified target situation, whereas extrapolation is an inference that says something *about the target situation*. Keeping these labels apart provides a clarified understanding of the problem. Second, I discuss different candidates to analyse effectiveness propositions and map them onto the distinction between 'efficacy' and 'effectiveness', which clinical researchers use to distinguish between causal claims that hold *within* a specific clinical trial and those which hold *beyond* respectively. It appears that effectiveness claims differ from efficacy claims only in scope. Using case studies and existing methodological work on pRCTs, however, I show that the sort of propositions that pragmatic trials establish not only differ in scope but in kind: pRCTs relate the *event of taking* or *prescribing a treatment* to the benefit for patients. Thus, unlike RCTs, they do not test the causal effects of medical interventions but rather

examine the causal chains from behavioural and social factors to relevant outcomes. I conclude by pointing out that pRCTs do not solve the problem of extrapolation, yet they add valuable knowledge on our way there.

Jonathan Fuller (Department of History and Philosophy of Science, University of Pittsburgh)

To Prevent, To Cure

The second half of the Twentieth Century saw the rise of a new preventive medicine, in which pharmacologic prevention – supplemented with individual lifestyle change – took up much of our medical consciousness, as drugs from statins to antihypertensives took over much of our medical spending. The concept of 'risk reduction' is central to this revolution. In this talk, I will further our understanding of prevention and risk and their relationship to cure. Rather than a conceptual analysis of these terms, I will focus on how we can model them towards a unified account of medical intervention.

Following Steel (2008), I will model mechanisms of disease pathophysiology using our best framework for causal modeling: directed graphs (Pearl 2009). The pathogenesis or etiologic mechanism of a disease can be represented by a graph with the disease as its most causally downstream node. Preventive medical interventions can then be modeled as 'ideal interventions' in Woodward's (2003) sense. Preventive interventions are ideal interventions on etiologic mechanisms that disrupt the mechanism somewhere upstream of the disease, removing the influence of farther upstream etiologic variables and setting the value of variable(s) at the site of intervention so as to lower the probability or risk of the disease. For instance, a statin drug interrupts the normal mechanism of cholesterol biosynthesis in the body in setting the amount of LDL-cholesterol in the blood to a lowered value, thus putatively lowering the risk of a downstream heart attack. Interventions that disrupt a mechanism at a bottleneck, a node through which all upstream causes influence the disease, have a greater risk-lowering potential. My account thus reconciles the causal concept of prevention with the probabilistic concept of risk reduction.

Moreover, through the lens of my account curative medical interventions are often not very different. I draw a distinction between etiologic mechanisms and constitutive mechanisms. In the medical context, etiologic mechanisms bring about a previously absent disease, while constitutive mechanisms maintain the presence of a disease as its 'constitutive causal basis' (Stegenga 2015). For instance, mechanisms of bacterial survival and reproduction in the lungs maintain the existence of bacterial pneumonia. A curative intervention is an ideal intervention that disrupts a constitutive disease mechanism, as when an antibiotic disrupts mechanisms of bacterial survival and reproduction in eliminating pneumonia.

The upshot is a unified account of medical intervention that sees preventive medicine as shifting the locus of medical intervention from constitutive to etiologic mechanisms.

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Gregor Greslehner (Department of Philosophy, University of Vienna & ImmunoConcEpT, CNRS UMR 5164, University of Bordeaux)

Quo vadis, immunology? Towards a new theory of immunological recognition

Contrary to the narrative commonly found in textbooks, immunological recognition and response turn out to involve more than just pattern recognition receptors binding pathogen-associated molecular patterns. Also modifications of that view, like the danger theory, fail to explain some immunological phenomena. Most importantly, there exist molecular patterns that are shared among pathogenic and non-pathogenic microbes that the immune systems appears to be able to distinguish and respond to in appropriate ways for a richer spectrum of physiological states than just danger or its absence. One way is to argue for "context" or additional molecular

signals. While this is certainly a promising model that needs to be made more precise, the focus on recognition of three-dimensional structures obstructs a broader, functional perspective.

At the same time, there is a growing body of evidence that microbial community structures are much more conserved with respect to their functional capabilities than their taxonomical composition – including the repertoire of their signature molecular motifs. Does this conservation of functions just emerge as an ecological colonization equilibrium or does the host's immune system play an active role in monitoring, maintaining, and modifying microbial functions? For this to be explained by physiological processes, the immune system ought to be able to recognize functions of microbes, not just structures that would be unique for specific microbial taxa or species.

Therefore, I suggest to move away from the exclusive focus on molecular structures and to consider the possibility of the immune system recognizing functional features. In addition to evolutionary arguments that there is a selection for functions rather than structures, I emphasize examples of physiological processes of the immune system which indicate that it cares less about "who is there" and more about "what is going on".

Even though "what is going on" may manifests itself structurally eventually, i.e., in the form of metabolites, signal molecules, interaction networks, effects on surrounding tissues, impacts on the host, etc., to still call all such monitoring of activities and functions of microbes 'recognition of structure' would require quite a stretch of the term 'structure', at least beyond the notion of directly recognizing three-dimensional structural motifs as indicative of certain microbial pathogens. But even beyond this modest conceptual shift, there is evidence in current scientific publications for sensors that can indeed directly recognize functions that can be carried out by a diversity of different structures, where it would be hard to maintain the view that a structure would be recognized, even if only indirectly. Thus, the philosophical shift to functions also aims at closing an explanatory gap in science.

I propose a conceptual clarification of the notions of *structure* and *function* that can be usefully applied to solving this puzzle. Which kind of structure or function is being recognized by the immune system has methodological consequences for immunological research. In this way, the philosophical contribution is intended to impact biomedical practice by shifting the focus of attention from structures to functions.

Laurence Huc (Toxalim, INRA & University of Toulouse)

What is a carcinogen? bridging the gap between basic biology and regulatory toxicology

The origins of cancer is a central question for biologists. Even if Rachel Carson established the link between chemical contaminated-environment and cancer occurrence in the 1960's (Carson, 1962), the hegemonic area of genetics gave the direction of research in oncology and carcinogenesis. From "back luck" origins (Tomasetti and Vogelstein, 2015; Tomasetti et al., 2017) to the genetic causes of cancer, the part of environment in the occurrence of this disease is a central point of debate regarding public health (Wu et al., 2015). What does it make controversy? Why is it so hard to define a carcinogen?
Through current events of controversies, with the example of persistent pollutants like dioxin and hydrocarbons and with the example of pesticides such as glyphosate, I will illustrate the definitions of a carcinogen, according to the point of view of a biologist, a toxicologist in basic science. I will also focus on the definition supported by the non-profit organization IARC (International Agency for Research on Cancer) and the marked discrepancy with the regulatory agencies like EFSA (European Food Safety Authority) and ECHA (European Chemicals agency) (ECHA, 2017). I will examine the proofs of carcinogenicity according to laws and citizens. Finally, I will analyse the influences of the private interests and think tanks on the scientific definition of a carcinogen (Demortain, 2018) and how science is deprived of its own produced knowledge (Oreskes and Conway, 2010).

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Simon Lohse (Centre for Ethics and Law in the Life Sciences, Leibniz University Hannover)

Scientific inertia in replacing animal experimentation in biomedicine

Millions of animals are used for basic and translational research purposes every year. In 2011 alone, more than seven million vertebrates and cephalopods were used in Europe. To reduce this number and to comply with the 3R-principle ("refine, reduce, replace"), animal rights activists, politicians and sympathetic life scientists have been promoting the development and use of alternative methods to animal experimentation based on cell and tissue cultures, organ(s)-on-a-chip technology and computer modelling (in short "non-animal-methods"). These efforts have, however, not led to an extensive replacement of animal experimentation in basic and translational science. In this talk, I will attempt to shed some light on this state of affairs with reference to key institutional and socio-epistemic barriers for the development and implementation of non-animal methods in the context of biomedicine. In the first part of my talk, I will provide some background regarding animal experimentation in Europe and sketch the current landscape of non-animal-methods. I will then highlight a number of institutional factors that inhibit the development and use of non-animal-methods. In the main part of my talk, I will turn to a socio-epistemic issue that has received some attention in the literature, namely the *relatively low* level of engagement of the scientific community in developing and promoting non-animal-methods. This situation is usually accounted for in two contrasting ways. The first way is based on the assumption (shared by many basic researchers) that animal experimentation is just indispensable for progress in biomedical science. Others (usually developers of non-animal-methods and activists) state that it is mainly dogmatism that inhibits the development and use of non-animalmethods. Both accounts, while containing some truth, fall short of explaining the complexity of the situation. For this reason, I will develop an alternative and more sophisticated explanation for the relatively low level of engagement of the scientific community which is based on insights from philosophy and sociology of science. More precisely, my talk draws on recent work on model organism research and scientific repertoires (Levy & Currie, 2015; Ankeny & Leonelli, 2016) and on the so called "risk-spreading-argument" (Kuhn 1959/D'Agostino, 2010). I will argue that the inertia in replacing animal experimentation in biomedicine is rooted (a) in secondary epistemic functions of animal-based systems of practice (such as anchoring research communities and establishing shared methods and standards) and (b) in the socio-epistemic logic of science in general. I will show that my account offers a deeper explanation of the relatively low level of engagement of the scientific community that can integrate the true aspects of the discussed "standard accounts".

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Mariusz Maziarz (Interdisciplinary Centre for Ethics & Institute of Philosophy, Jagiellonian University)

Causal pluralism in medicine and its implications for clinical practice

The purpose of the study is twofold. First, I argue that biomedicine accepts moderate causal pluralism as an epistemic definition of causality. Second, investigate the implications of the pluralism of notions of causality for

clinical practice. I differentiate among 'actions' that do not change the relata of causal claims, (mechanistic) 'interferences,' and 'interventions' *sensu stricte* that act on causes to change effects. My central claim is that causal claims presupposing diverse concepts of causality can deliver evidence for different types of evidence-based policy.

The current philosophical views on what is the meaning of causality presupposed by biomedical research are vastly divided. The differentiation may indicate that the results of reconstructing the view on causality presupposed by biomedical researchers depend on the choice of case studies. This implies that different biomedical studies presuppose different concepts of causality. I use referentialist semantics as a tool for studying the meaning of causal claims in biomedicine and take the types of relations that can be discovered with research methods used in a given study as the reference of causal-family words present in the causal claim put forward by researchers.

The argument proceeds with case studies that are representative of the main approaches to causal inference in contemporary biomedicine. First, I analyze the Centre for Disease Control and Prevention (CDC) search for the cause of EVALI (vaping-related lung injury) (Blount et al. 2019) and relate it to the regularity view on causality. Second, I reconstruct the probabilistic view on causality from Reichenberg et al. (2006) cohort study of paternal age and ASD. Third, I analyze the research of Ratnayake et al. (2018) on the influence of blue light on age-related macular degeneration in humans and relate it to the mechanistic view on causality. Fourth, I study the RECORD trial (Home et al. 2007) aimed at assessing the effectiveness of rosiglitazone and interpret it as presupposing a version of the manipulationist view on causality. Given this, moderate causal pluralism is a stance adequate to research practices in medicine. However, accepting different epistemic concepts of causality has severe implications for clinical decisions.
I argue that the evidence for regularity and probabilistic relations suffices for 'actions' that do not modify the relata of causal claims. The reason is that the possibility of confounding cannot be excluded. This allows for undertaking evidence-based decisions even without the knowledge of full causal structure. What follows, putting observational studies at the bottom of the evidence pyramid is not justified for the actions that do not require knowledge of invariance under intervention. In contrast, mechanistic causal claims do not warrant the success of interventions because the represented mechanism may be screened off by other mechanisms. Finally, clinical trials allow for estimating average treatment effects that suffice for putting forward type-level causal claims that are invariant under intervention and therefore conducting 'interventions' in the strict sense. My work can also serve as an example of using referential semantics to study the meaning of philosophical concepts implicitly used in sciences.

Elena Rondeau (ImmunoConcEpT, CNRS UMR 5164, University of Bordeaux)

Understanding cancer progression and its control: An analysis of immune contribution to metastasis

Ongoing progress in cancer research is improving our comprehension of the spatial and temporal complexity of tumour progression, indeed characterised by the pleiotropic involvement of the tissue environment at different stages and scales (Plutynski 2018), from the tumour milieu (or "micro-environment") to the host organism (or "macro-environment"). While supplementing our thorough appreciation of the cell-intrinsic properties of transformation, these advances still face serious difficulties, such as those linked to tumour recurrence and systemic spread.

Metastasis is currently the leading cause of cancer mortality, correlating with disease severity and resistance to conventional therapy. Beyond its accepted description as a multistep process resulting in the development of secondary tumours at distant sites, certain observations remain partly unexplained and conceptually challenging. One striking example is the report of organ specificity for secondary growth, which accounts for the apparent tropism of cancer cells migrating from a given primary tumour toward particular metastatic tissues.

The "seed and soil" theory of metastasis, initially coined by British surgeon Paget (1889), stipulates that such patterns may be due to favourable interactions between circulating tumour cells (the "seed") and specific microenvironments encountered during their dissemination (the "soil"). Historically, this hypothesis was soon replaced by a mechanical explanation centered on the anatomy of vascular connections leaving the primary site (Ewing 1929). Metastasis research in the early twentieth century adopted the latter proposal in its experimental designs, before the definitive refutation of mechanical exclusiveness. Paget's forgotten analogy then resurfaced as an appropriate and testable account for secondary organ selectivity (Fidler 2003).

The historical dynamics of this debate and its conceptual implications may directly participate to shaping current research hypotheses concerning metastatic tropism, as the "seed and soil" analogy has been, and presently is, extensively cited and re-interpreted in the scientific literature. Moreover, its premises and consequences could also benefit from a revisited analysis in the light of recent clinical and experimental observations. In particular, the evidence of distant "pre-metastatic niche" preparation reveals anticipatory signalling in the dissemination process, through the establishment of a tumour-promoting milieu in the secondary organ before the arrival of cancer cells (Chin 2016). This involves both tumour-derived factors and pre-existing host components, thus refining our consideration of secondary organ specificity.

Crucial in this reappraisal is the aim to decipher the implication of the immune system in cancer progression, given the delicate balance between its protective and pro-tumoral activities. Indeed pre-metastatic processes are frequently associated with immune cell recruitment and inflammation, which directly participate to tumour development and spread. Some populations of immunosuppressive and pro-invasive immune cells may actively foster "seed" persistence and enable distant metastasis by establishing a hospitable and/or attractive environment in future "soils".

Hence the pressing question of determining the exact role of host immunity in metastasis causality: to what extent, and how, do the immune actors of cancer progression contribute to the preparation and specificity of secondary sites? I propose to complement this examination with an experimental approach, conducted in a mouse model of breast cancer known to specifically disseminate to the lungs.

Michel Shamy (Departments of Medicine & Epidemiology, University of Ottawa & Ottawa Hospital Research Institute)

The Evidential Problem of Randomized Clinical Trials: Assessing Physicians' Beliefs

How much scientific knowledge is required before it is permissible to launch a randomized clinical trial (RCT)? This is what we might call the *evidential problem* of clinical trials, and it is of course a difficult methodological (and ethical) problem subject to layers of contentious debate. John Lantos, for instance, has recently argued that:

Any RCT comparing usual practice to an alternative would be deeply offensive. To do such studies, doctors would have to admit to themselves and to their patients that ... they really do not know which treatment is best. They would need to believe that so strongly that they would be willing to assign treatments at random rather than by using their own clinical judgment and medical expertise. (Lantos, 2020)

At the same time, it by now a familiar trope in the debates over the reliability — or unreliability; see, e.g., (Zarin et al., 2019) — of biomedical research that, in nearly all cases, no amount of clinical research can provide certain knowledge about which treatment is best. Assigning treatments at random is sometimes all that can be done *because of* the state of the background medical evidence — as when, for instance, past studies indicated that the expected effects of new treatments are small, or the patient population exhibits behavioural or physiological complexities that make clean predictions about efficacy possible. In certain cases, randomization can be preferable to doing nothing whatsoever.

The debate, as we say, is complicated. So much so that we have become skeptical that an answer to the evidential problem can be implemented. Accordingly, to try to test this concern, we conducted a series of studies which aimed to organize and describe physicians' beliefs about how much evidence, and what kind of evidence, is needed in order to enroll patients in randomized clinical trials. We would like to present data from two of our studies at the conference.

In the first study, we conducted a series of interviews with chairs of research ethics boards as well as clinicial researchers (primarily in stroke research), and philosophers of science. We asked our participants to define the kinds of uncertainty that they believed to be necessary in order to conduct a randomized trial, and we also asked our participants if they could operationalize their definition. Our interviews yielded 8 logically distinct definitions of the relevant uncertainty, suggesting that beliefs about the evidence that is needed prior to launching a RCT are heterogenous.

Our second study consists of a systematic review of the literature on clinical trials, again focusing on the kinds of uncertainty that authors mentioned as being necessary in order to permit a RCT. The results of this study were broadly consistent with those of the first: we observed 5 logically distinct definitions of uncertainty that captured 70% of the observations that we analyzed. Again, this suggests that beliefs about the amount and quality of evidence that is needed prior to launching a RCT are heterogenous.

Together, our studies seem to confirm our worry. Even if it can be conclusively shown that a particular type of evidence is what *should* be considered necessary and sufficient for beginning a RCT, our studies indicate there is what might be called an *implementation challenge* — attention must be paid to how researchers and policy-makers with varying beliefs about clinical trial evidence can reorient their beliefs around evidence before the relevant evidential standards can be implemented.

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Devora Shapiro (Philosophy Faculty, Southern Oregon University)

Medical Outliers, Intersectional Subjects, and the Peculiar Failure of the Differential: A Proposal for Improvement

Zebras may be rare in comparison to horses, globally speaking, but in the right contexts (or continents) they are not so unlikely to be the source of hoofbeats. So too with our medical outliers – patients whose symptoms defy common explanation, and whose response to treatment fails to conform to standard expectations. In this paper I suggest that our difficulty in identifying and treating such patients – medical outliers – is rooted in a dissonance between the phenomena we hope to capture and the frameworks for representation and evaluation that we have available; on the one hand we have the statistically rare diseases or disorders that we wish to identify and treat, and on the other we have a framework for diagnostic methodologies that is based on likelihoods and wide-ranging commonalities.

Our diagnostic methodologies largely rely on large scale trends occurring in statistically significant population groups. Our rare diseases and disorders, however, are rare because they are statistically uncommon. In this presentation, therefore, I illustrate the need for alternative frameworks – structural representations - for the evaluation and diagnosis of uncommon diseases and/or medical conditions. Specifically, I discuss the benefits of approaching diagnosis and the diagnostic process through a reflexive model that considers the "constellation of symptoms" at one end, and on the other end conceptualizes patients as intersectional, multiply constructed subjects: biosocial phenotypes. In doing so, I demonstrate the potential for benefit that such an approach has to offer for the individual medical outlier. I further note the extended potential for such an approach to have application at the population level, particularly with regard to vulnerable, disadvantaged, or underserved unique and place-based communities.

I illustrate my point using the case of myalgic encephalomyelitis (ME) – a disease initially identified as "benign" and later as a psychosocial manifestation of hysteria, but that is currently understood to be a permanent, physically disabling condition related to inflammation of the brain and presenting with myriad verifiable and measurable symptoms.[1] ME, having long been connected with Chronic Fatigue Syndrome (CFS), had until recently been repeatedly dismissed as a real or legitimate disease beyond the psychological. This dismissal has largely been attributed to three factors: 1) the predominance of the disease in females; 2) the variation in the presentation and epidemiology of the disease; and 3) the lack of explanation for the mechanism or etiology of the disease.

Having demonstrated the underlying issue as illustrated through the case of ME, I discuss the proposed framework and approach to diagnosis. The approach offered addresses the basic concern represented by statistically driven diagnostic algorithms and utilizes an achievable approach to information that can be implemented utilizing available technological resources. Further, I suggest it also offers flexibility with understanding "individual patients" as well as "patient populations," and promises improved responsiveness to concerns realized in vulnerable or disadvantaged communities and persons.

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Jonathan Sholl (ImmunoConcEpT, CNRS UMR 5164, University of Bordeaux)

Mobilizing Biogerontology and Immunology in the Project of Theorizing Health

This presentation starts from the observation that while specific and localized theories abound within medical research, there is still no general theory of health. This is quite shocking due to the level of explanatory precision that the biomedical sciences have obtained since the birth of physiology as a science, but also due to the presence and number of general theories within a variety of other sciences, e.g. relativity, thermodynamics, evolution, etc. The question becomes: if the medical sciences were to develop such a theory, what would it look like and where would it come from? As this is clearly a large problem, I will only sketch some initial suggestions that may be helpful going forward. I will first briefly mention some reasons as to why there is no general theory of health and why the many theories that do exist tend to get obscured by philosophers who have traditionally focused primarily on conceptual definitions. I will then draw on philosophical work on medical theories to sketch some desiderata for assessing a given candidate and will suggest the use of philosophical tools that can be helpful in theory construction, e.g. furthering the project of a scientific metaphysics (of medicine). One obvious candidate could be 'homeostasis', but even though this remains a central concept for physiology, it has not been the basis of a more general explanatory theory of health. I will argue instead that there are at least two ostensibly fruitful areas that could support health theory construction: biogerontology and immunology. The former helps formulate a way to think about health through time (optimizing trade-offs), while the latter may help think through what it is that is healthy (e.g. via an immunological account of what constitutes an organism). The scope and specificity in these areas make them rather promising for operationalizing the vague construct of health by integrating existing physiological knowledge on multiple levels, providing robust explanations with sufficient granularity, and generating useful predictions. The downside is that much conceptual confusion remains in each field, calling for further interdisciplinary investigation.

Kari Theurer (Department of Philosophy, Trinity College)

Disorder As Dysfunction: Adaptationism and Teleology in Psychiatry

The concept of *dysfunction* plays a central role in psychiatry, and particularly in analyses and definitions of psychiatric disorder. Both the DSM and the ICD characterize disorder, in part, in terms of dysfunction, as syndromes characterized by clinically significant symptoms that reflect "a dysfunction in the psychological, biological, or developmental processes that underlie mental and behavioural functioning".[1] A similar clause appears in the DSM 5. The "dysfunction clause" is now also built into the NIMH's Research Domain Critieria (RDoC) Project, the goal of which is to "understand the nature of mental health and illness in terms of varying degrees of dysfunctions in general psychological/biological systems."[2]

Each of these definitions and descriptions includes, as a necessary condition, the idea that any putative disorder must reflect an underlying psychological, biological, or developmental dysfunction. It is this clause, and particularly the concept of biological dysfunction, that is the focus of this paper. These accounts lack an analysis of the concept of *dysfunction*, without which we are left with no satisfactory way to distinguish between genuine dysfunction and healthy or neutral variations in how people think, feel, and behave. This is of crucial importance for a manual that purports to catalogue and taxonomize legitimate disorders, rather than normal variations in the population. Accounts of dysfunction inevitably rely on some underlying account of *function*. In this paper I consider whether the account of function implicit in naturalistic accounts of psychiatric disorder can and should do the work that psychiatry demands. This account is what would ultimately do the work of demarcating genuine dysfunction from normal variation in biological functioning, and thus would serve as the ultimate justification for inclusion a psychiatric nosology.

I argue that naturalistic accounts of psychiatric disorder grounded in the failure of biological function are implicitly adaptationist: that is, such accounts assume that the mechanisms governing the "normal" or "healthy" (non-disordered) psychiatric functioning of a person are the products of natural selection. Moreover, I argue that this adaptationist assumption is not only conceptually misguided but also unsupported by the available evidence. I begin by articulating the connection between the concepts of function, dysfunction, and disorder in psychiatry. I then outline two influential accounts of the relationship between disorder and dysfunction, and argue that at least

one of those must ultimately understand the function of a trait to consist in the effects for which it was naturally selected. I argue that this renders such accounts adaptationist. I then offer some theoretical considerations from evolutionary biology against the assumption that the mechanisms responsible for healthy or non-disordered psychiatric functioning are necessarily adaptive, and show that this implicit adaptationism falls well short of the requisite standards of evidence in evolutionary biology for showing that a trait is an adaptation. I conclude by explaining why it matters whether psychiatry is ultimately adaptationist: it matters because it ultimately amounts to a dangerous reintroduction of teleology into psychiatry by way of the uncritical acceptance of certain mistaken assumptions about evolution, its mechanisms, and its products.

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1 World Health Organization. 2018. *International Classification of Diseases*. Similar language appears in the American
Psychiatric Association's DSM 5.
2 https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/index.shtml

Katherine Valde (Philosophy Department, Wofford College)

Using Metaphysics to Institutionalize Pluralism

There is a growing recognition among scientists and philosophers that metaphysical presuppositions guide scientific research. These metaphysical presuppositions guide scientific research by articulating an ontology for a particular domain of phenomena, that is, by making a claim about what sort of things there are and what they are fundamentally like. These ontological claims, in turn, prescribe a particular methodology for how to go about investigating and explaining those kinds of things. There is thus what I call a move from metaphysics to methods.

A key question that has yet to be addressed is what sort of attitude ought to be taken towards such metaphysical presuppositions. Scientific research cannot take place in a metaphysical vacuum, and there are a variety of different attitudes one can take towards these frameworks, as exemplified by recent cancer research.

This presentation will begin by examining how current cancer research, which is largely centered on Somatic Mutation Theory (SMT), grows out of a mechanistic metaphysical picture of the world and how that mechanistic framework limits methodological choices to those that the make use of mechanistic concepts. Next, I will examine the newly proposed processual alternative to this approach. The processualists argue that mechanistic accounts are inadequate because they presuppose an incorrect metaphysical picture of the biological world. I will argue that there is an important problem with the argument from metaphysics to scientific methods. For example, the processualists are calling for an unwarranted limitation of our scientific methods. My objection is not to processualist research per se, but to grounding cancer research exclusively on a any singular metaphysical framework. Instead, I argue that metaphysical frameworks are underdetermined by empirical research, and thus we should turn to the important pragmatic aims of science to ground a genuine explanatory and methodological pluralism for cancer research.

While an agnostic attitude towards metaphysical frameworks could help to ground a genuine pluralism of research frameworks placing this metaphysical burden on individual researchers misses the more systemic issues causing siloed research agendas. This presentation will argue that interventions at a higher level will be more effective in bringing about pluralism in practice. For example, providing training on the underdetermination of metaphysical frameworks by empirical research and inductive risk to grant reviewers could help to ensure a diversity of programs operating on a variety of metaphysical frameworks are funded and executed.

I close my argument by highlighting the importance of institutionalizing the pluralism. Given the inductive risk for large non-epistemic consequences in cancer research, pragmatic values need to play a role in our reasoning about what sorts of research to pursue. Rather than making these metaphysical arguments to individual researchers, making them to government and industry sources of funding is the most promising route to achieving a productive pluralism.