Where do Personalized Health Technologies stand today?

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Abstract: In June 2018, experts met at ETH Zurich to discuss technological challenges in advanced cell systems, variant interpretation, novel therapeutics and the integration of clinical data. The translation of these technologies into innovative clinical approaches in oncology, immunology, infectious diseases, neurology and cardiology will be a challenge for the future. Detailed information at http://www.personalizedhealth.nexus.ethz.ch/

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Progress in the laboratory representation of clinical material opens up novel possibilities for discovery and diagnostics offering new opportunities for patients. Thanks to the combination of ‘omics’ technologies, bioinformatics, and statistics with cell biology, high-throughput screening, and chemical biology it is now possible to carry out empirical projects with a very large scope. International sharing of data and methods made such projects conceivable and has given them feasible turnaround times.

Evolution of Clinical Trials in the Era of Precision Medicine and Immunotherapy

Lillian L. Siu, MD, FRCP, is a senior medical oncologist at Princess Margaret Cancer Centre and Professor of Medicine at the University of Toronto. As she says, clinical trials remain the most important tool for addressing relevant questions and bringing new therapies to patients. “The paradigm of sequential phase I to II to III clinical trial evaluations of novel cancer therapeutics has undergone a shift in recent years, as the urgency of bringing promising new treatments to patients challenges the efficiency of a serial, stepwise drug developmental path”. She used several examples to illustrate clinical trial design frameworks that have evolved over the past decade. As she points out, clinical trials must demonstrate meaningful benefits in either selected patient subsets or larger patient groups, trials that identify small incremental gains are no longer considered acceptable. “Many of these new trial designs can also be adaptive in nature, and this concept will become more relevant in the conduct of emerging trials.” As defined by Pharmaceutical Research and Manufacturers of America, adaptive trials are “a clinical study design that uses accumulating data to decide how to modify aspects of the study as it continues, without undermining the validity and integrity of the trial.” Looking forward, ‘next-generation’ clinical trials will also need to be adaptive at an individualized level, targeting the dynamic status of tumors and taking intra-tumoral heterogeneity into consideration in their design, such as the application of liquid biopsies or other serial tumor collections to track changes.

Lillian L. Siu, MD, FRCP, Princess Margaret Cancer Center

Progenitor Cells and Organoids in the Translational Research of Prostate Cancer

Prostate cancer (PCa) is the most frequently diagnosed cancer in men and a major cause of morbidity and mortality. Although PCa can be effectively diagnosed and staged using combinations of serum prostate-specific antigen (PSA), digital-rectal examination and imaging, its features vary between patients in ways that cannot be detected by these tests. “This makes it difficult to identify individuals who are at greatest risk of disease progression, metastasis and death”, says Marianna Kruithof-de Julio, PD Dr phil and Head of the Urology Research Laboratory at the University of Bern. “Improved screening approaches to stratify patient populations could allow earlier and more precise identification of patients at risk of relapse and the selective application of more aggressive treatment strategies prior to widespread tumor dissemination.” It is true that metastasis initiating cells (MICs) are cancer cells that drive the metastatic lethal phenotype. A better understanding of the underlying biology of MICs is needed to provide tools for assessing patient risk and creating targeted therapies. However, little is known about the heterogeneity of MICs and whether subpopulations of MICs carry markers linked to a high risk of metastatic disease. “Our aim is to elucidate the molecular characteristics and heterogeneity of MICs and surrounding cells in prostate cancer. In order to achieve this, we have used multiple distinct preclinical models, including organoids, ex vivo maintenance of needle biopsies, zebrafish xenografts, and
microvasculature grown on a chip. These complementary models are robust, fast and provide personalized, clinically relevant information on MICs and therapy response. We have generated patient-derived xenografts (PDX) of primary and metastatic PCa and patient-derived organoids from needle biopsies. We have also developed and implemented a clinically relevant culture system for studying tumor tissue ex vivo. This technique makes it possible to cultivate tumor slices and needle biopsies in a tissue culture setting without loss of normal architecture, viability, proliferative properties, or expression of specific markers. And she continues: “We have shown that the effects of drug treatment in this system are consistent with those observed on organoids (in vitro) and PDXs (in vivo). Organoids derived from established PDX models have been tested for their response to the standard care compounds enzalutamide and docetaxel at different cell densities as part of pilot experiments for the establishment of automated high throughput screens at NEXUS Personalized Health Technologies. Our preliminary data indicate that higher drug efficacy (enzalutamide and docetaxel) is achieved and directly correlates to higher cell densities (range of 1000 to 1750 cells). Finally, we have customized a microvasculature-on-a-chip device to mimic the bone microenvironment as a model to study cancer cell extravasation (Fig. 1). Briefly, bone marrow-derived mesenchymal stem cells (hMSC) and umbilical endothelial cells (HUVEC) are seeded in the microfluidic device embedded in fibrin gel. The self-assembled vascular network forms within 5–7 days. The vessels are open and perfusable and, when introduced, cancer cells can flow through the vascular network and extravasation can be tracked over time by fluorescent and bright field live microscopy. This methodology is complemented by in vivo characterization of tumorigenic properties of organoid-forming cells in zebrafish xenografts.”

Marianna Kruithof-de Julio, PD Dr. phil, Inselspital University Hospital Bern

Data and Computing Services for Personalized Health: A Paradigm Shift

Dr Diana Coman Schmid works in Scientific IT Services at ETH Zurich. Her talks aim to give a user and usage perspective on handling sensitive biomedical data in secure computing environments in the context of the Swiss Personalized Health Ecosystem (SPHN/PHRT projects and beyond). “The specific context is established by the patient data, which is subject to high legal and ethical requirements, but also presents major and challenging computing demands”, as she puts it. “Secure and powerful IT infrastructures for data storage, computing and sharing are essential for offering top-class services for personalized healthcare research.” And she describes: “Leonhard Med operated by Scientific IT Services at ETHZ, is an example of a secure computing and data platform for personalized healthcare designed to address the requirements and challenges of sensitive biomedical data handling. While secure infrastructures are instrumental, they are not sufficient. What we also need in this diverse and dynamic data ecosystem are innovative teams with interdisciplinary expertise (for example in medicine, molecular biology, computer science, bioinformatics, statistics, IT, law, ethics, etc. see Fig. 2). Since the user experience is a major focal area, the challenges revolve around finding the right balance between security and usability.”

Dr Diana Coman Schmid, ETH Zurich

Research & Services in Personalized Health > need Hybrids

Why: prevent, diagnose and treat unfavorable health conditions more precisely
Who: hybrid ecosystem: medical, IT, computational and statistical experts, legal, ethics
How: security, data storage, management and analysis; data exchange & interoperability

Fig. 2. Diana Coman Schmid, ETH Zurich. Data & computing services for personalized health: a paradigm shift.

Prolonging the Life of Patients with Metastatic Lung Cancer through Targeted Treatments

The treatment of metastatic Non-Small Cell Lung Cancer (NSCLC) has improved dramatically in recent years according to PD Dr Alessandra Curioni, Head of Thoracic Oncology at the Division of Oncology, Department of Hematology and Oncology of University Hospital Zurich. In her view, this is thanks to the advances made in molecular analysis tools, which have led to the discovery of targetable oncogenic molecular abnormalities. “Targeted therapies have significantly improved outcomes for patients with NSCLC who carry activating mutations in the epidermal growth factor receptor (EGFR) gene or translocations in the anaplastic lymphoma kinase (ALK) gene or c-ros oncogene 1 (ROST). Moreover, the first targeted treatment for NSCLC harboring the BRAF V600E mutation has been recently approved. However, several other oncogenic drivers have been identified in NSCLC that do not yet have approved targeted treatments”, she tells us. “In addition to this approach, treatment with immune checkpoint inhibition with anti-PD-1 therapy has proven to be successful in advanced NSCLC and has changed standard practice in multiple settings. However, the majority of unselected patients fail to respond and patient selection is therefore fundamental.” But as she knows: “Emerging biomarkers have been recently described which will enable us to select patients for immunotherapy. PD-L1 expression by immunohistochemistry (IHC) is the most commonly used marker. Tumor mutational burden (TMB) is currently being explored as a clinical biomarker and has been assessed in patients’ tumors or blood. Immune checkpoint inhibition has been most successful in tumor types such as melanoma, NSCLC and bladder cancer that have a high mutagen exposure-related mutational burden. This is due to the potential neo-antigens that could result from somatic mutations and which could elicit a specific immune response. TMB might therefore become an additional method for selecting patients who might benefit significantly from checkpoint inhibition, but this needs still to be prospectively demonstrated.” Very recently, combinatorial treatments involving anti-PD1 and anti-PDL1 and chemotherapy have proven to be promising; however, there is still more work...
to be done to obtain a better understanding of the biomarkers of benefit for specific combinations and how treatment-sequencing will impact the survival of patients with advanced NSCLC. To do this, she has developed a new clinical trial of combinatorial treatments based on her preclinical studies (Fig. 3). Moreover, she is establishing a comprehensive biobank of material from lung cancer patients undergoing immunotherapy for the purpose of understanding the mechanisms of response and resistance to these treatments for further therapeutic applications.  

Alessandra Curioni, University Hospital Zurich

Fig. 3. Alessandra Curioni, University Hospital Zurich. Prolonging the life of patients with metastatic lung cancer through targeted treatments.

**CAR T Cells: Engineering Immune Cells to Treat Cancer**

Carl H. June, MD, has news about his specialty, CAR T cells. He predicts that the emergence of immuno-oncology as the first broadly successful strategy for metastatic cancer will force clinicians to integrate this new pillar of medicine with the existing pillars of chemotherapy, radiation and targeted small molecule compounds. “Chimeric antigen receptor (CAR) T cells have proven that engineered immune cells can serve as a powerful new class of cancer therapeutics. Adoptive immunotherapy retargeting T cells to CD19 via a chimeric antigen receptor (CAR) is an investigational treatment capable of inducing complete tumor regression of B-cell malignancies when there is sustained survival of infused cells.” The Director of translational research at the Abramson Cancer Center at the University of Pennsylvania is convinced that clinical experience has helped to define the major challenges that have to be met in order to make engineered T cells a reliable, safe, and effective platform that can be deployed against a broad range of tumors.

“The emergence of synthetic biology approaches for cellular engineering provides the field with a broadly expanded set of tools for programming immune cells. We want to know how these tools could be used to design the next generation of smart T cell precision therapeutics.”

In solid tumors, he has observed antitumor activity in patients with ovarian cancer, pancreatic ductal adenocarcinoma, pleural mesothelioma and glioblastoma following the infusion of CAR T cells expressing scFv specific for mesothelin or EGFRvIII. “However, this approach has not yet resulted in complete tumor eradication”, he reminds us. “Using genome edited T cells, it may be possible to enhance and prolong the activity of T cells that have disrupted immune and metabolic checkpoints. In preclinical studies, we show that TCR-specific T cells have enhanced antitumor activity following disruption of TCR alpha and beta genes and the PD1 gene using CRISPR/Cas9. This approach is just entering a clinical trial. These findings provide insights into the immunobiology of effector T cells and demonstrate the potential of multiplexed CRISPR/Cas9 genome editing to synthetically enhance the efficacy of immunotherapy.”

Carl H. June MD, CAR T cells

Approaching Personalized Medicine in Multiple Sclerosis Care

Multiple sclerosis, a disease of the nervous system in which the myelin sheath of neurons is damaged, is the specialty of Prof Dr Andreas Lutteroti, Assistant Professor of Experimental Therapies Research at University Hospital Zurich.

“Achieving personalized treatment decisions is particularly important in chronic diseases that are caused and influenced by a combination of genetic, environmental and lifestyle factors that often lead to high variability of disease courses”, he explains. “It is this complexity of diseases at biological and clinical level that eventually impedes personalized decision-making in medicine. Multiple sclerosis (MS) is a prototypic complex disease characterized by chronic inflammation of the brain and spinal cord. MS predominantly affects young adults who consequently carry a high risk of future disability.”

A characteristic feature of the disease is its heterogeneity in clinical presentation, imaging findings, pathophysiological processes, pathology and treatment responses. Also, the number and efficacy of available therapies for MS has increased considerably in recent years. However, it has been associated with increased risks for patients and thus demands carefully balanced treatment decisions. Identification of reliable parameters for predicting disease course, relapses, disability progression and treatment responses represents a clear unmet medical need in MS care. As the member of the Clinic for Neurology says: “In the last couple of years we have built a collaborative consortium in Zurich with the Clinical Research Priority Program (CRPP) to address the various aspects of disease heterogeneity in MS, combining biological and imaging parameters to correlate with disease course and treatment responses.” Successful individualization of MS care can be facilitated by implementing new tools for continuously monitoring patients in their personal environment using smartphones and wearable sensors, and by integrating biomedical data using computational models and machine learning approaches to predict risk at the individual patient level.

Lutterotti is excited about the new prediction models which will allow clinicians to stratify patients accordingly and verify treatment responses at individual level. “This will ultimately modify the way we approach chronic diseases as we move into the era of precision medicine.”

Prof Dr Andreas Lutteroti, University and University Hospital Zurich

A Cancer Precision Medicine Program Driven by Multi-omics, Analytics and Modeling

Dr Olivier Elemento faces a challenge with his precision medicine program for oncology care in the near future. “We are concentrating our activities on whole-exome sequencing for patients with advanced tumors, as we believe that precision medicine has greater scope to assist these patients, who have limited clinical options left. The hope is that genomics will help
us to identify additional treatment possibilities.” The renowned computational biologist plays a leading role in the precision medicine initiative at Weill Cornell Medicine, the medical school of Ivy league member Cornell University. As Director of the Caryl and Israel Englander Institute for Precision Medicine at Weill Cornell Medicine, he and his group are pioneering entirely new approaches that combine Big Data analytics with experimentation to help prevent, diagnose, understand, treat and ultimately cure cancer (Fig. 4). He is well aware that precision medicine relies on computational biology to interpret genomic data and that applying this approach to each individual patient is fraught with challenges. “Looking at a patient’s cancer genome, we discover many mutations and it’s not always obvious how to associate them with a particular response to treatment. But thanks to computational biology and artificial intelligence, we can discover correlations between mutations and response to a specific treatment, the extreme effect of which is the response to immunotherapy”, says the Associate Professor and Director of the Institute for Computational Biomedicine. “Immunotherapy checkpoint inhibitors only work well in about 20% in solid tumors. Today it is hard to know ahead of time which patients will respond to immunotherapy.”

By analyzing tumors from a large number of patients treated with immunotherapy and using techniques inspired by artificial intelligence, his group is identifying biomarkers of response to immunotherapy”, says the Associate Professor and Director of the Institute for Computational Biomedicine. “Immunotherapy checkpoint inhibitors only work well in about 20% in solid tumors. Today it is hard to know ahead of time which patients will respond to immunotherapy.”

Moreover, the researchers find that it is not only the number of mutations present in the tumor that is important to immunotherapy response, but also the kind of genes expressed within the tumor and the story they tell about the kinds of immune cells existing within the tumor. He calls it ‘gene-expression deconvolution’. And he concludes: “When sequencing a tumor you also measure the expression of genes coming from the immune cells, not the tumor. When you look at the expression signature of specific immune cells, you recognize the type of immune cell populations within the tumor and how diverse these immune cells are. Our conclusion is that when we combine this type of immune characterization with tumor mutations and exposed peptides, we will be able to find out who may respond to immunotherapy.”

And what are his plans for the next few years? “We will increasingly start sequencing the entire genetic make-up of tumors, not only the coding genes, using what we call whole-genome sequencing. We will also be better able to dissect the complex micro-environment of tumors using high-throughput single cell measurements”, predicts the specialist in cancer systems biology. However, when we just determine the complete DNA sequence of a tumor’s genome, we do not know what is driving the cancer, especially if it is metastasizing. Tumors evolve as they move from site to site, and that’s just one of the problems. Therefore we have to identify the driver mutations in both the primary and metastasized tumors.” His strategy is a very ambitious one, but could provide patients with more therapeutic options.

Olivier Elemento, Weill Cornell Medical College

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**Fig. 4. Olivier Elemento, Weill Cornell Medical College. A cancer precision medicine program driven by multi-Omics, analytics and modeling.**