ETH zürich

Personalized Health 2020

29 and 30 June 2020
Virtual Only

nexus
Personalized Health Technologies

Abstracts of Speakers presented at the

Personalized Health Technologies 2020

29 and 30 June 2020

Conference Organizer:

nexus
Personalized Health Technologies

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Monday 29 June 2020

10:00–10:15	Welcome Address	
Session 1	**Immuno Oncology**	**Shana Sturla (ETH Zurich)**
The session 1 keynote is scheduled for today at 15:50		
10:15–10:40	Michal Bassani *Proteogenomics and immunopeptidomics for the development of personalized cancer immunotherapy*	
10:40–10:45	Tech Slam Cytvia – David Pointu *Explore the diversity of cancer tissue section by IF multiplexing with Cell DIVE*	
10:45–11:10	Alessandra Curioni *Success and challenges of immune-checkpoint inhibitors for the treatment of lung cancer*	
	Short Break	
11:35–12:00	Rodrigo Vazquez-Lombardi *Harnessing CRISPR-Cas9 genome editing for the functional engineering of T cell receptors with minimal cross-reactivity*	
Session 2	**Advanced Cell Systems**	**Christian Stirnimann (ETH Zurich)**
13:00–13:25	Nicolas Broguiere *Reconstruction of the tumor microenvironment to improve the phenotypic stability of human colorectal cancer tumoroids*	
13:25–13:30	Tech Slam Fritz Gyger AG – Sabrina Dällenbach *CERTUS FLEX for dispensing droplet microarrays*	
13:30–13:55	Furkan Gökçe *Physiologically relevant drug-screening approaches to personalize leukemia treatments*	
13:55–14:20	Christian K. Hirt *Discovery of alternate treatment options for pancreatic cancer using automated high-throughput screening on patient-derived organoid lines*	
	Coffee Break	
14:35–15:35	Senthil Muthuswamy Keynote *Tumor organoids for cancer biology and personalized medicine*	
15:35–15:50	Tech Slam Berkeley Lights – Mio Muelthaler *Directly test individual T cell function with fewer cells*	
15:50–16:50	Meromit Singer Keynote Session 1 *From Characterization Towards Function: Systemic Aspects of T Cell Immunity in Cancer and Autoimmunity*	
	Closing Remarks	

Tuesday 30 June 2020

Session 3	**Clinical Decision Making**	**Gunnar Rätsch (ETH Zurich)**
09:00–10:00	Caroline Uhler Keynote *Causality and Multi-Domain Data Integration in the Light of Drug Repurposing for SARS-CoV-2*	
	Coffee Break	
10:15–10:40	Stefan Stark *SCIM: universal signle-cell matching with unpaired feature sets*	
10:40–10:45	Tech Slam PHRT – Francois Curtin *The future of Personalized Health: Building Bridges*	
10:45–11:10	Michael Baudis *Beacon v2 – Towards felixible use and clinical applications for a reference genomic data sharing protocol*	
	Short Break	
11:35–12:00	Emilie Pasche *SVIP-O, the Swiss Variant Interpretation Platform for Oncology*	
Session 4	**Novel Therapeutics**	**Karl-Heinz Altmann (ETH Zurich)**
13:30–13:55	Roger Schibli *An academic platform for translational radiotracer development for non-invasive imaging*	
13:55–14:00	Tech Slam Enamine – Andrey Tarnovski *New dimension for drug discovery*	
14:00–14:25	Anna Popova *Enabling precision oncology: highly miniaturized chip-technology for testing live patient-derived cancer cells with anti-cancer compounds to reveal individual drug sensitivity and resistance*	
	Coffee Break	
14:40–15:40	Prashant Mali Keynote *Improving genome interpretation and gene therapeutics: new approaches and new challenges*	
	Closing Remarks	

Proteogenomics and immunopeptidomics for the development of personalized cancer immunotherapy

Michal Bassani
University and University Hospital Lausanne

The remarkable clinical efficacy of the immune checkpoint blockade therapies has motivated researchers to discover immunogenic epitopes and exploit them for personalized vaccines and T cell based therapies. Mutated human leukocyte antigen binding peptides (HLAp) are currently the leading targets. We and others have shown that the direct identification of tissue-derived immunogenic neoantigens by mass spectrometry (MS) is feasible. However, most studies attempt to identify neoantigens based on HLA binding prediction tools. We have compiled a large immunopeptidomics database across dozens of HLA allotypes. By taking advantage of co-occurring HLA-I alleles, we rapidly and accurately identified HLA-I binding motifs. We have shown that training HLA-I ligand predictors on refined motifs significantly improves the identification of neoantigens. Recently, we have acquired the largest reported HLA-II immunopeptidomics dataset. We introduced novel algorithmic tools to analyze this data and developed HLA-II epitope prediction tool trained on immunopeptidomics data that results in major improvements in prediction accuracy.

In contrast to the private neoantigens, tumor-specific antigens that are shared across patients may be more attractive for immunotherapy. Recent studies have focused on the discovery of aberrantly-expressed non-canonical antigens, which expands the repertoire of targetable epitopes through the translation and presentation of presumably non-coding regions. However, their identification requires highly sensitive and accurate MS-based proteogenomics approaches.

We have developed a novel analytical pipeline that can precisely characterize the non-canonical HLAp repertoire. The workflow incorporates whole exome sequencing, both bulk and single cell transcriptomics, ribosome profiling, and a combination of two MS/MS search tools with group-specific false discovery rate calculations for accurate HLAp identification. We identified more than 400 non-canonical HLAp derived from the expressed lncRNAs, transposable elements and alternative open reading frames, including an immunogenic peptide derived from an open reading frame downstream of the melanoma stem cell marker gene ABCB5. Moreover, non-canonical HLAp were experimentally confirmed to be shared across tumors through targeted MS, by which synthetic heavy isotope-labelled peptides were spiked into the peptidomic sample. This analytical platform holds great promise for the discovery of novel cancer antigens for cancer immunotherapy.

Explore the diversity of cancer tissue section by IF multiplexing with Cell DIVE

David Pointu
Cytiva

Cell DIVE is an imaging solution which targets cancer applications and the characterization of a patient's tumor microenvironment and immune system response. 400 antibodies have been validated and it allows the imaging of up to 60 biomarkers from a single tissue to understand cellular distribution and phenotypes.

Success and challenges of immune-checkpoint inhibitors for the treatment of lung cancer

Alessandra Curioni
University Hospital Zurich

Despite the presence of tumor-specific T cells in cancer patients, the tumor usually escapes immune control. Co-inhibitory molecules such as PD-1 are expressed on T cells upon their activation and prevent the immune response from overshooting during infections. PD-1 is therefore often referred to as immune checkpoint molecule. In the context of cancer, however, such molecules prevent protective effector responses. The ligand for PD-1, namely PD-L1 is expression on tumor cells and prevent PD-1 expressing T cells from performing their cytotoxic function. The majority of PD-1 T cells in the tumor are characterized with reduced effector functions and are functionally exhausted. T cell exhaustion is reversible and anti-PD-1/PD-L1 antibodies block the co-inhibitory signal and reinvigorate the effector function of antigen-experienced CD8 T cells in the tumor. Monoclonal antibodies targeting the PD-1/PD-L1 inhibitory pathway (named immune-checkpoint inhibitors, ICI) show good clinical activity in several malignancies with an overall response rate from 15 to 34%. For lung cancer, the use of such treatments has dramatically improved the outcome of patients with metastatic disease. ICI can be given as monotherapy or in combination with chemotherapy in the first and further line setting and response rates have reached more than 50%. Despite this success, no all patients respond to ICI and selection of patients is crucial. The routinely used marker in the clinical setting is PD-L1. However, PD-L1 expression is not stable and be altered by the use of chemotherapy. Another marker under investigation is the "tumor mutational burden". Immune response against tumor cells require the presence of neoantigens and tumor-specific CD8 T cells in order to kill tumor cells. Different T cell clones found in various cancer types can recognise mutated gene products, which can lead to tumor control. Interestingly, lung cancer patients with a high TMB show improved progression free survival compared to patient with a low TMB. After initial responses, patients can still develop resistance (acquired resistance) which might be tumor-intrinsic or extrinsic. This knowledge is essential for the development of future treatments.

Directly test individual T cell function with fewer cells

Mio Muelthaler
Berkeley Lights

Since the beginning of 2020, the Lightning Desktop system is now available in the EU (the first system is already installed at the DKFZ in Heidelberg). This Lightning system allows you to comprehensively characterise T-cells within 24 hours by providing:
– Measurement of secreted cytokines (IL-2, TNFα, IFNγ,...)
– Membrane markers (e.g. CD137, CD63)
– Providing kinetic data to differentiate slow and fast killing T cell phenotypes (potency/ exhaustion)
– cDNA for accessing correlations between sequencing data (NGS) and phenotype

All of this happens at the single-cell level simultaneously and under identical conditions which allows for time-lapse imaging.
Further information is available here:
https://www.biorxiv.org/content/10.1101/204693v1
https://www.berkeleylights.com/products-services/lightning

Harnessing CRISPR-Cas9 genome editing for the functional engineering of T cell receptors with minimal cross-reactivity

Rodrigo Vazquez-Lombardi
ETH Zurich (D-BSSE)

T cell receptor (TCR) gene therapy is a promising cell therapy approach for the treatment of cancer. However, the identification of TCRs that target tumor-associated self-antigens with sufficiently high strength for effective TCR gene therapy remains a challenging and time-consuming process. Furthermore, engineering of low-avidity TCRs for enhanced tumor targeting is complicated by the high propensity of TCRs for cross-reactivity and the lack of a direct correlation between TCR affinity and function. In this context, engineering TCRs using antigen-binding display technologies suffers from important limitations, most notably TCR cross-reactivity towards host antigen, which can lead to severe and adverse side effects, including patient death.

Here, we report the TCR-accepting T cell (TnT) platform for the functional engineering and cross-reactivity screening of TCRs. The TnT platform was generated through multistep CRISPR-Cas9 genome editing of a human T cell line and incorporates fully-defined genomic changes allowing for the homogenous and physiological display of TCR libraries. Functional selections coupled with deep sequencing allowed us to identify TCR variants with enhanced recognition of the cancer-testis antigen MAGE-A3, but that display negligible cross-reactivity to both known and newly identified off-targets. Furthermore, we provide important insights into the discordance between TCR binding and signaling, and into the emergence of cross-reactivity in engineered TCRs. We envision the TnT platform as a valuable tool for the engineering of tumor-reactive TCRs with enhanced function and safety profiles for TCR gene therapy applications.

Reconstruction of the tumor microenvironment to improve the phenotypic stability of human colorectal cancer tumoroids

Nicolas Broguiere
Swiss Federal Institute of Technology Lausanne (EPFL)

Colorectal cancer (CRC) is the third most deadly cancer for each sex. Patients with metastatic disease have a ≈14% five-year survival rate, with only half of the patients responding to standard oxaliplatin/5FU-based chemotherapy. Targeted therapy options are very limited: anti-EGFR mAbs are applicable only to patients that are not KRAS/BRAF mutated (≈50%), anti-VEGFA mAb being the only approved alternative. New treatment strategies are therefore urgently needed. Both their development and the selection of patients likely to be responders would benefit from phenotypically accurate CRC models.

Traditional cancer cell lines and patient-derived xenografts (PDX) have only limited predictive power because of the strong phenotypic drifts induced by the immortalization and culture on 2D plastic, or the growth in a mouse tumor microenvironment (TME), respectively. Tumoroids, miniaturized *in vitro* cancer tissues derived from patient-derived tumor cells in 3D matrices, have raised tremendous hope as models that capture more faithfully the patho-biological programs underpinning carcinogenesis. However, existing tumoroids lack key components of the TME and it has not yet been explored to which extent tumoroids phenotypically match their native counterparts.
Here we employed single-cell RNA sequencing (scRNA-seq) to systematically compare patient-derived (i.e.'non-cultured') CRC tissues with their corresponding tumoroids. We found that the cell type diversity found in native tumors was largely lost in tumoroids, which lacked cells from the TME as well as some specific tumor cell populations. Moreover, the gene expression profile of *in vitro* grown cells was also significantly altered.

To improve the phenotypic accuracy of CRC tumoroids, we reconstruct the TME *in vitro* by isolating and simultaneously expanding cancer cells, fibroblasts, lymphocytes and macrophages from the same donor, which can then be recombined in defined co-cultures. The non-cellular components of the microenvironment – cytokines, growth factors, oxygen tension, matrix, physical properties – are also systematically evaluated. Highly parallelizable transcriptomics methods are used to monitor in depth how cancer cells interact with the reconstructed TME and compare to the original tumor.
We anticipate that this study will lead to next-generation tumoroids, bearing key TME components, that will better mimic CRC and thus open up exciting perspectives for drug discovery and personalized medicine.

CERTUS FLEX for dispensing droplet microarrays

Sabrina Dällenbach
Fritz Gyger AG

The CERTUS FLEX is a precise and flexible liquid dispenser, which can dispense a broad range of reagents, cells and other fluids at high speed. Both, high and low viscous fluids can be dispensed using micro valve technology with volumes <50 nl upwards. The flexible design allows numerous applications such as the droplet microarray from Aquarray, this combines the solution-based synthesis of compound libraries with high-throughput biological screenings. Here, the CERTUS FLEX has been proven to be well suited to dispense tiny volumes of HeLa-CLL2 cells. Subsequent analysis demonstrated a homogenous cell distribution, good cell viability and normal cell morphology.

Physiologically relevant drug-screening approaches to personalize leukemia treatments

Furkan Gökçe
ETH Zurich (D-BSSE)

Despite improvements in the survival rate of acute lymphoblastic leukemia (ALL), different genetic subtypes, and the number of relapses still lead to a high mortality rate [1]. The identification of new and targeted therapies for genetic subtypes is hindered by the scarcity of robust models and by the low number of patients presenting high-risk subtypes. In particular, cell-line-based models feature a genetic landscape that deviates from that of the patients. However, the genetic landscape is fundamental for the selection of effective therapeutic interventions. Therefore, it is of paramount importance to develop a method that can recapitulate the actual patient status for therapy selection.

Recently, patient-derived xenografts (PDX) of ALL cells have been used to predict patient-specific drug responses in vitro in well-plate-based assays [1, 2], which indicates that patient-derived leukemia cells can provide information to personalize treatments for high-risk patients. To maintain the viability of PDX-ALL cells in vitro, a co-culture with bone-marrow cells (MSC) is needed [2]. While currently used approaches constitute important steps towards personalized treatment selection, they (1) do not recapitulate drug metabolism effects, and, thus, cannot be used to predict the efficacy of prodrugs, and (2) do not include flow conditions that are experienced in vivo by the ALL cells. To address these shortcomings, we developed a microphysiological drug-screening platform, which enables to co-culture PDX-ALL cells, human liver microtissues, and MSCs to mimic liver-mediated drug metabolism in a microfluidic environment.

The platform features a straight microfluidic channel interconnecting multiple tissue compartments, which feature funnel-shaped tissue loading ports. The tissue compartments are elevated from the channel bottom to minimize direct physical interaction between the PDX-ALL cells in the channel and the liver microtissues. Two large medium reservoirs are located at the ends of the microfluidic channel to enable multi-day assays without the need for daily medium exchange. Tilting of the chip actuates the flow to transport metabolites and nutrients in the microfluidic channel. The tissue-loading ports, located above the tissue compartments, ensure air exchange and simple loading of liver microtissues. The inlet positions are compatible with 384-well plate standards for easy handling.

Discovery of alternate treatment options for pancreatic cancer using automated high-throughput screening on patient-derived organoid lines

Christian K. Hirt
University and ETH Zurich

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive malignancy with a mortality rate above 98%. Currently the only curative therapy for PDAC is surgical resection. Due to late disease detection, this is only suitable for about 20% of all patients. Therapeutic options for locally advanced or metastatic PDAC are therefore needed. In recent years, patient derived organoids (PDOs) from tumor tissues have been developed. Compared to 2D cancer cells lines, these models better incorporate the cellular dynamics and phenotypes of PDAC.

We established a human PDAC organoid biobank, which broadly recapitulates the phenotypic and mutational spectrum of primary pancreatic cancers and reflects differential drug sensitivities observed in patients. In a fully automated drug-repurposing screen with over 1'000 FDA-approved compounds we identified several drugs that effectively target PDAC organoids, which could be confirmed in several additional PDO lines. In follow up studies we showed that the identified hits reduce tumor growth in vivo in patient-derived xenograft (PDX) models. Within the validated compounds were drugs that inhibit HIF-1α signalling, a pathway that protects PDAC cells under hypoxic conditions and that is frequently upregulated in PDAC patients and organoid lines.

Our study provides proof-of-concept for drug screening in tumor organoids to establish precision and translational medicine approaches for pancreatic cancer.

Tumor organoids for cancer biology and personalized medicine

Senthil Muthuswamy
Dana-Farber / Harvard Cancer Center

Growing cells in three-dimensional (3D) culture conditions has been in use for several decades. However, neither the interest to use 3D culture methods nor the necessity is fully appreciated until recently. Developments in the ability to design organ-specific media conditions to support the growth of primary or stem or tumor cells in 3D culture conditions have catapulted the field to a new dimension and the appetite for using 3D culture methods is now overshadowing the use of monolayer cultures. For the past 20 years, my laboratory has developed and utilized 3D culture and organoid methods to understand epithelial morphogenesis, cell polarity, cancer initiation, and progression and translational cancer research. I will discuss our efforts in developing and using 3D culture methods for tumors and stem cells for modeling and understanding cancer biology. In addition, I will discuss our recent unpublished observations on the use of tumor organoid cultures for personalized medicine.

From Characterization Towards Function: Systemic Aspects of T Cell Immunity in Cancer and Autoimmunity

Meromit Singer
Dana-Farber Cancer Institute / Harvard Medical School

The introduction of single-cell high-throughput measurement technologies (such as single-cell RNA-seq) have recently transformed the breadth and depth at which the immune component within tissues can be characterized and studied. Specifically, the ability to characterize heterogeneity of cellular states within tissues and the changes that occur following disease or therapeutic intervention are enabling the formation of novel prognostic tools as well as hypotheses regarding cellular function. Excitingly, the recent ability to generate coupled RNA-seq and TCR / BCR data at single-cell resolution and at high-throughput (using 10X technology) has enabled exploring relationships between cellular states and clonal distributions within and across tissues.

In this talk we will discuss systemic aspects of T cell immunology at homeostasis and during cancer or autoimmune disease, as they are revealed with coupled single-cell RNA-seq and TCR annotation. We will first discuss cross-organ Th17 heterogeneity during homeostasis, and how it changes upon induction of EAE disease. We will show that Th17 clones found in different organs upon disease originate from different transcriptional states within the spleen, indicating different classes of clonal migration and/or expansion across organs. Next, we will present a study in which we assess the extent to which peripheral blood can be used for tracking a host response to tumor by characterization of the CD8 + T cell tumor-directed component in blood in an immunogenic mouse model as well as a cohort of melanoma patients. Last, we will present COMET, a novel computational tool the Singer group has developed to identify marker panels for cell populations of interest (e.g. identified from single-cell RNA-seq data). We describe how COMET is built to assists in the transition from cellular characterization with single-cell RNA-seq to functional studies, and its availability as a tool to the broad community.

Causality and Multi-Domain Data Integration in the Light of Drug Repurposing for SARS-CoV-2

Caroline Uhler
ETH Zurich

Massive data collection holds the promise of a better understanding of complex phenomena and ultimately, of better decisions. An exciting opportunity in this regard stems from the growing availability of perturbation/intervention data (drugs, knockouts, overexpression, etc.) in biology. In order to obtain mechanistic insights from such data, a major challenge is the integration of different data modalities (transcriptomic, proteomic, structural, etc.). I will first discuss our recent work on coupling autoencoders to integrate and translate between data of very different modalities such as sequencing and imaging. I will then present a framework for integrating observational and interventional data for causal structure discovery and characterize the causal relationships that are identifiable from such data. We end by demonstrating how these ideas can be applied for drug repurposing in the current SARS-CoV-2 crisis.

SCIM: universal signle-cell matching with unpaired feature sets

Stefan Stark
ETH Zurich, Swiss Institute of Bioinformatics, Life Science Zurich Graduate School, PhD Program Molecular & Translational Biomedicine

Recent technological advances have led to an increase in the production and availability of single-cell data. The ability to integrate a set of multi-technology measurements would allow the identification of biologically or clinically meaningful observations through the unification of the perspectives afforded by each technology. In most cases, however, profiling technologies consume the used cells and thus pairwise correspondences between datasets are lost. Due to the sheer size single-cell datasets can acquire, scalable algorithms that are able to universally match single-cell measurements carried out in one cell to its corresponding sibling in another technology are needed. We propose Single-Cell data Integration via Matching (SCIM), an approach to recover such correspondences even in the absence of overlapping features and in the presence of large numbers of observations in two or more technologies. SCIM assumes that cells share a common (low-dimensional) underlying structure and that the cell distribution is approximately constant across technologies. It constructs a technology-invariant latent space using an auto-encoder framework with an adversarial objective. Multi-modal datasets are integrated by pairing cells across technologies using a customized bipartite matching scheme that operates on the low-dimensional latent representations. We evaluate SCIM on cellular data simulated from a temporal branching process and show that the cell-to-cell matches derived by SCIM reflect the same pseudotime on the simulated dataset (Pearson's coefficient: 0.86). Moreover, we apply our method to two real world scenarios, a melanoma tumor sample and a human bone marrow sample, where we pair cells from a scRNAseq dataset to their sibling cells in a CyTOF dataset achieving 93% and 84% cell-matching accuracy for each one of the samples respectively. SCIM is a scalable and flexible algorithm that bridges the gap between generation and integrative interpretation of diverse multi-modal data.

The future of Personalized Health: Building Bridges

Francois Curtin
Personalized Health and Related Technologies

The ETH Domain Personalized Health & Related Technologies initiative is presented with its programs and some highlights for its developments are discussed.

Beacon v2 – Towards felixible use and clinical applications for a reference genomic data sharing protocol

Michael Baudis
University of Zurich

Beacons provide discovery services for genomic data using the Beacon API developed under the leadership of ELIXIR, as a key driver project of the Global Alliance for Genomics and Health (GA4GH). The Beacon protocol itself defines an open standard for genomics data discovery. It provides a framework for public web services responding to queries against genomic data collections, for instance from population based or disease specific genome repositories. Sites offering beacons can scale through aggregation in "Beacon Networks", which distribute single genome queries among a potentially large number of international beacons and assemble their responses.

As part of ELIXIR's Beacon 2019–21 project work has started on a radically re-designed Beacon protocol, with the aim to provide a maximum of flexibility while closely adhering to data and security standards promoted by the international research community, and especially as part of projects in the GA4GH ecosystem. Upcoming features have been designed with view to biomedical applications, e.g. for variant evidence and annotation data or the retrieval of phenotype and other clinical data when used in secure (network) environments. Recently, the efficient use of the Beacon protocol for non-human genome data has been demonstrated for COVID-19 repositories, showcasing the flexibility of the protocol.

Here I will provide an overview about the history, current status future directions of the Beacon protocol, including details about the Beacon+ service on top of the progenetix.org cancer genomics resource.

SVIP-O, the Swiss Variant Interpretation Platform for Oncology

Emilie Pasche
HES-SO / HEG Geneva, SIB Swiss Institute of Bioinformatics

After several years of collaboration to improve and harmonize the next-generation sequencing practices in somatic mutation calling, a number of Swiss hospitals, pathology institutes and the Swiss Institute of Bioinformatics members have pointed to a set of shortcomings, most prominently the lack of a central repository for clinically verified variant annotations in cancer. Therefore, the Swiss Variant Interpretation Platform for Oncology (SVIP-O) was developed to propose a centralized, joint and curated database for interpretation of clinical somatic variants. Swiss hospitals and related institutions will have the possibility to easily submit batch of variants to the platform. The first version of the system is constituted of a public interface to browse variants annotations, gathered from a large set of publicly available resources (e.g. ClinVar, CIViC, etc), as well as a curation interface to assess evidences about variant annotations. The curation process is supported by advanced text mining tools, which triage and annotate literature to facilitate its curation by Swiss-Prot curators. The first release of SVIP-O will be deployed in June 2020. In a later version, a review interface will be added to the platform, thus enabling clinical experts to ensure a consistent assessment of pathogenicity.

New dimension for drug discovery

Andrey Tarnovski
Enamine Ltd.

Enamine Ltd was founded in 1991 with the advent of high throughput screening in early drug discovery. The driving force of the company's development was rapidly increasing demand for new chemical compounds. Having an advantage of a significant number of building blocks allowed Enamine to pioneer the market and to take a leading position with currently over 225,000 stock-available building blocks, growing by 2,000 newly synthesized items every month. Since year 2000 the company established a high throughput synthesis laboratory, which allowed rapid growth of the screening collection to over 2.7 million compounds. The synthesis technology was built on the accumulating of the in-house synthesized building blocks that would be repeatedly used in different library syntheses. Enamine offers a wide portfolio of carefully designed Fragment Libraries, Discovery Diversity sets and Targeted Libraries, such as Antiviral, RNA targeted, Nucleoside Mimetics, CNS, PPI, etc. The company's well-established compound management facility, including robotic and acoustic dispensers, allows delivery of the compound libraries in any suitable format, such as dry samples or DMSO (DMSO-d6) solutions of required concentration in plates of preferred type, including assay-ready Echo-dispensed microplates.

In addition to its stock collection of screening compounds Enamine offers a unique chemical space of 1.2 Billion synthetically feasible structures – "REAL Database", enumerated on the basis of Enamine's Building block collection and the pool of over 160 in-house validated combinatorial protocols. As an extension of REAL Database Enamine provides access to over 13 Billion non-enumerated highly feasible structures with a possibility of convenient similarity search, thus enabling exceptional opportunities for hit follow-up and lead optimization projects. Introduction in Enamine's service portfolio biology services CRO "Bienta" in 2011 allowed offering of integrated drug discovery services - from hit finding, expansion through lead optimization and ADME profiling, and till the advanced lead candidate. Enamine has been actively developing custom synthesis service since 2004 helping the clients to advance their discovery chemistry projects. Having the world's largest building blocks collection and proven experience in chemical synthesis, Enamine became a preferred chemistry supplier to numerous big pharma, biotech and agrochemical companies, academic institutions and research centers, as well as to petrochemical, nutrition and fragrance industries across the globe.

An academic platform for translational radiotracer development for non-invasive imaging

Roger Schibli
Paul Scherrer Institut

Functional imaging of biological and pathological processes at a molecular level using positron emission tomography (PET) offers an unparalleled opportunity for personalized medicine in the future. With this Technology Transfer Project (TTP) we improve the availability of radionuclides and radiotracers for clinical studies we have established and improved the radiopharmacy platform to facilitate the production of innovative radiotracers according to Good Manufacturing Practice (GMP) for clinical studies. As part of the improvement, we installed automated radiosyntheses modules at the Paul Scherrer Institute as well a solid target station at the 18 MeV medical cyclotron of the ETH Hönggerberg.

Till today the TTP has produced the radiotracers: i) [18F]-AV1451 (to detect Tau-pathy in Alzheimer's patient) for ongoing clinical studies at the USZ, HUG and CHUV; ii) [18F]-AzaFol (targeting the folate receptor on tumor cells) for a multi-center, first-in-man study at the USZ, CHUV and the Cantonal Hospital St. Gallen; iii) [18F]-PSS-232 (targeting the mGluR5) for a clinical study investigating glutamate release after N-acetylcystein challenge and; iv) [177Lu]-PP-F11N a optimized minigastrin analog against the cholecystokinin receptor 2 expressed on medullary thyroid cancer. Over all more than half a dozen clinical studies were enabled and facilitated with the support since the start of the TTP within the PHRT initiative. We will present selected examples of the translational research activities from-bench-to bedside.

Enabling precision oncology: highly miniaturized chip-technology for testing live patient-derived cancer cells with anti-cancer compounds to reveal individual drug sensitivity and resistance

Anna Popova
Karlsruhe Institute of Technology

Cancer is the second leading cause of mortality worldwide and resulted in 8.8 million deaths worldwide in 2015. Today's common practice is for cancer patients to undergo therapy without having been examined for individual sensitivities or resistance of tumor cells to certain anti-cancer drugs. This leads to the fact that more than half of the patients do not respond to the therapy. Testing the sensitivity of patient-derived tumor cells ex vivo in so-called Drug Sensitivity and Resistance Test (DSRT) can help to determine the appropriate treatment for each patient and spot the development of resistance to a given therapy. However, the number of cells obtainable from a biopsy is often insufficient for performing ex vivo tests in conventional microtiter plates. In our laboratory, we have developed a Droplet-Microarray (DMA) platform, which is based on a hydrophilic-superhydrophobic patterned surface and allows for formation of arrays of stable separated droplets of nanoliter volume. We have established the DMA platform as a system for compound screening of live cells that enables screening of only 100 cells per concentration in 100 nL droplets. Recently, we have tested our platform for screening of primary patient-derived cancer cells and demonstrated that the dose-response of as few as 100 primary patient-derived chronic lymphocytic leukemia (CLL) cells to anti-cancer compounds on the Droplet-Microarray platform resembles that of the dose-response obtained in 384-well plates requiring 20,000 tumor cells per experiment. Here we are going to present our developments and plans in establishing miniaturized DMA-based DSRT, which we perform in cooperation with University Hospital Heidelberg. We believe that miniaturized DMA-based DSRT has a potential to be implemented in medical practice for precision medicine.

Improving genome interpretation and gene therapeutics: new approaches and new challenges

Prashant Mali
University of California San Diego

Abstract: The recent advent of RNA-guided effectors derived from clustered regularly interspaced short palindromic repeats (CRISPR)–CRISPR-associated (Cas) systems have dramatically transformed our ability to engineer the genomes of diverse organisms. As unique factors capable of co-localizing RNA, DNA, and protein, tools and techniques based on these are paving the way for unprecedented control over cellular organization, regulation, and behavior. However efficaciously achieving these objectives will entail research and development of aspects including and beyond the CRISPR-Cas systems. In this seminar, I will describe some of our ongoing efforts in this regard.

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