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Commentary

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Novel Formulation of Cannabinoid Analogues Treating DLBCL and MCL

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Introduction

Cell and gene therapies are seen as the next frontier in medicine as they have the potential to bring cures to patients that suffer from life-threatening diseases without many treatment options available to them. The idea that a patient's own cells can be reprogrammed to replace or eliminate faulty genes or to attack cancer cells in a way that is not naturally possible is giving hope to many. In 2017, we have seen several approvals from these innovative medicines, Kymriah, Yescarta and Luxturna to name a few. However, a key challenge for all players and drug-makers in this field remains to be addressed: The cost of manufacturing is critically high due to the nature of these highly personalized medicines. This high cost greatly limits the number of patients that can be eligible and threatens the sustainability of the therapy as a whole, and this is likely to be reflected in the already high price tags of these drugs for the foreseeable future. In his presentation, Andreas would like to show the way these medicines are manufactured and delivered to the patients could have significant and disruptive implications for the future of healthcare. He will be sharing his vision and innovative technologies that could reduce the cost of these medicines significantly and make them accessible to a larger number of patients.

Advantages RNA analysis provide insight into diseases, molecular identification of body fluids and mechanisms leading to death and might develop into a valuable tool for identification of the cause of death in forensic pathology. Further potential uses are the determination of the age injuries of wounds and of the post-mortem interval. In this proof-of-concept pilot study clarifies and explains principles, applications and methods by offering a comprehensive and complete overview of using mRNA markers for estimating blood deposition time which can help to evaluate the time of the crime in forensic RNA work. Study presented in this thesis aimed to estimate the time passed since blood stains found in the crime scene by calculating the time of deposited blood using particular mRNA markers and unraveling one of the principles of at what time–when during the day or night a biological evidence was left at the scene–by applying the insights from circadian biology to some open forensic cases. By analyzing 4 candidate mRNA markers expression in peripheral blood samples collected from 29 health males. The four mRNA were collected from healthy persons for the duration of the 24 hours' day/night interval under four different groups, i.e. night/early, morning early morning/morning, morning/afternoon and afternoon/night.

This study identified 2 mRNAs with statistically significant expression rhythms which are MKNK2 and PER. It's found that, in general mRNA-based estimation of time categories was less accurate. The value of mRNA was demonstrated for blood deposition timing and introduced a statistical model for estimating day/night time categories based on molecular biomarkers, which shall be further validated with additional samples in the future.The recent years have seen the emergence of both ground-breaking scientific developments in high-resolution, high-throughput data gathering technologies enabling cost-effective collection and analysis of huge, disparate datasets on individual health, as well as of sophisticated clinical bioinformatics or machine learning tools required for the analyses and interpretation of this wealth of data. These developments have triggered numerous initiatives in Precision Medicine (PM), a data-driven and currently still, essentially a highly genome-centric initiative. Proper and effective delivery of PM poses numerous challenges. Foremost, PM needs to be contrasted with the powerful and widely used practice of Evidence-Based Medicine (EBM). The latter is informed by meta-analyses or group-centered studies from which mean recommendations are derived. These amount at first approximation to a "one size fits all" approach, whose major limit is that it does not provide adequate solutions for outliers. Yet, we are all outliers for one or another trait. In contrast to EBM, one of the strengths of PM, which focuses on the individual, lies in the area of individualized management, and this includes outliers. To achieve these objectives, it will be necessary to bridge PM and EBM. Through the collection, analyses and sharing of standardized medically relevant data globally, evidence-based PM will shift progressively from therapy to prevention, thus leading eventually to improved, clinician-to-patient communication, citizen-centered healthcare and sustained well-being. We will discuss challenges and opportunities towards these goals.

From the Orphan Drug Act of 1983, a rare disease is a condition that affects fewer than 200,000 people in the United States. In the European Union, the condition must only affect fewer than 1 in 2,000 people. While the numbers seem small, there is an estimated 350 million people that suffer from rare diseases, with 25-30 million belonging to the US alone and so far there have been over 7,000 different rare diseases identified. To put this in perspective, there are more Americans affected by rare disease than for HIV, Heart Disease or Stroke combined. It is important to understand that by nature rare diseases are difficult to diagnose, and consequently are not tracked. Thus, it is hard to accurately determine the number of rare diseases and their impact on a population. The average length of time from onset of symptoms to an accurate rare disease diagnosis is nearly 5 years, and patients see an average of over 7 different physicians before a diagnosis is made. This delay in diagnosis results in chronic physical, emotional and socioeconomic burden to both the patient and their family. A European Cost of Illness Study interrogating published literature on the cost of 10 selected rare diseases found that overall; the availability of data on economic burden for rare diseases was correlated with the availability of therapies, not the severity of the disease. Also, most rare diseases reviewed were found to have significant economic burden and indirect costs (many associated with loss of productivity) exceeded the level of direct costs. Rare Genomics has served over 500 undiagnosed patients since 2011, helping them access next generation sequencing to accelerate their pathway to a cure.

We have seen the same patterns reported for rare diseases in our own patients including heterogeneous disease marked by a range of severity across a variety of biological systems.

The most common systems affected are Neurologic, Respiratory, Gastrointestinal, Muscular and Cardiovascular. The average RG patient has also seen a range of physicians, the top three specialties consulted are: Neurologist, Clinical Geneticist, Ophthalmologist and Gastroenterologist. Lastly, undiagnosed/rare disease patients typically have already undergone a gamete of testing, the most common tests are: MRI, DNA Microarray and Single/Panel Sequencing. Because 80% of rare disease are genetic in origin, we hope that by providing support and access to next generation sequencing, we can help reduce the time and burden these families must undergo before identifying appropriate treatment for their disease. Novel Formulation of Cannabinoid Analogues Treating DLBCL and MCL: Diffuse Large B-Cell Lymphoma (DLBCL) and Mantle Cell Lymphoma (MCL) represent the most common and most aggressive forms of Non-Hodgkin Lymphoma (NHL) respectively. With CB1 antagonists as potential therapeutics for both DLBCL and MCL, we formulated VYR-206, developed from existing obesity treatment Rimonabant by the addition of our tetraazacyclic (N4) conjugate derivative.

This allows the potential for image guided theranostic application for diagnosis, precision and assessment of therapeutic response through radiotracer chelation. Our study is aimed at demonstrating VYR-206 activity in DLBCL and MCL for sensitivity or resistance. Cells from representative DLBCL and MCL cell lines were plated at 5,000 cells per well. The cells were incubated for 72 hours in 20 µL medium with 10% FBS and varied concentrations of experimental cannabinoid antagonist VYR-206, Rimonabant, or dimethylsulfoxide (DMSO). Viability assays were conducted using Celltiter-Glo Luminescent Cell Viability Assay. Experiments were performed 2-3 times independently, with concentration tested in triplicate. Most DLBCL cell lines treated with VYR-206 had a reduction in viability at concentrations of 50 µM or greater with few cells line displaying limited response even at concentrations of 100 µM. Increased variability is seen among MCL cell lines treated with VYR-206, most having a reduction of viability at concentrations of 25 µM or greater, with few cell lines at concentrations of 50µM and 2 cell lines showing no response even at concentrations of 100 µM. The discrepancy in response in both DLBCL and MCL may be due to genetic variability among cell lines.