Identification of tumor-specific antigens to decipher clonal heterogeneity, diagnostics tools and as targets to direct tumor-specific therapies (Case study #1)

Acute Myeloid Leukemia (AML) remains notoriously difficult to treat. Therapy-resistant cells escaping treatment frequently cause relapse of disease, and many studies therefore focus on the identification of such relapse-initiating cells. In contrast to previous dogma, AMLs manifest themselves within individual patients with remarkable heterogeneity. Multiple, genetically distinct AML subclones can coexist. Clonal heterogeneity is far from stable and can change over time or as a consequence of treatment. This strongly complicates current therapy, which mostly entails a "one size fits all" approach that is clearly not sufficiently effective. Within the UMCG Department of Hematology, a novel technology was developed to identify and prospectively isolate genetically distinct subclones within individual patients as viable cell populations. Quantitative proteomics was performed on a large panel of primary AML patient samples, which uncovered AML-specific expression profiles of plasma membrane proteins[1]. Antibodies against a large panel of these proteins have been validated, and are now implemented in the routine diagnostic pipeline. Moreover, these markers are considered for implementation in diagnostic pipelines in other hospitals.

Future studies will be aimed to extend the crosstalk between basic and clinical research with a focus on
i)   investigating the epigenetic states and transcriptional networks that are operational in these genetically distinct subclones within patients;
ii)   identifying more effective subclone-specific drug combinations, to be tested in vitro and in vivo in our humanized niche leukemia xenograft clinic;
iii) improving AML diagnosis, minimal residual disease detection and the detection of relapsed disease using our marker profiles;
iv)   studying the functional role of AML-specific plasma membrane proteins in further detail; and
v)   translating this knowledge into novel personalized treatments with the ultimate aim of delivering the right drug to the right cell. The discovery of AML-specific plasma membrane antigen expression profiles now enables various 'flavors' of immunotherapy. Current research lines include the evaluation of antibody-drug conjugates, and the generation of CAR-T cells directed towards AML-specific antigens. With regard to the latter, it is important to note that within the Department of Hematology a recent ZonMW/The Dutch National Health Care Institute grant was awarded (30m€) for the in-house development of anti-CD19 CAR-T cells for the treatment of DLBCL patients. CliniMACS Prodigy platforms have now been established at the UMCG in order to generate CAR-T cells, and the aim is to further develop cell therapeutics in the field of AML in the future as well.

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1   de Boer B, Prick J, Pruis MG , Keane P, Imperato MR, Jaques J, Brouwers-Vos AZ, Hogeling SM, Woolthuis CM , Nijk MT, Diepstra A, Wandinger S, Versele M, Attar RM, Cockerill PM, Huls G , Vellenga E, Mulder AB, Bonifer C, Schuringa JJ. Prospective isolation and characterization of genetically and functionally distinct AML subclonmes. Cancer Cell. 2018, 34: 674. Doi: 10.1016/j.ccell.2018.08.014

Implementation of new anti-cancer drugs (Case study #2)
Societal Relevance & Impact Example

Cancer is the second leading cause of death globally and 1 in 6 die from cancer. Increasingly, patients with cancers can be adequately treated if diagnosed early and if treatments are available. An overwhelming number of new drugs is being developed with varying degree of efficacy. Importantly, the costs associated with these new drugs are extremely high, challenging the sustainability of oncological patient care.

In 2015, the European Society for Medical Oncology (ESMO) launched the ESMO-Magnitude of Clinical Benefit Scale (ESMO-MCBS) to facilitate improved decision-making. The ultimate goal is to promote access to high value cancer treatments and therewith to reduce unfair situations for patients. Knowledge on the best cancer treatments should be accessible for all people around the world.

Since its introduction, the ESMO-MCBS has received wide-spread international attention not only from clinicians and health care policy makers, but also from pharmaceutical companies and politicians. Scientific publications reporting on the use of the ESMO-MCBS are among those receiving the highest impact (as measured by Altmetric scores). Currently, the ESMO-MCBS is being implemented on a more international scale and studied as a model template for evaluating drugs for other indications outside oncology.

UMCG professor Elisabeth de Vries was the leading person of the ESMO Cancer Medicines Committee and the ESMO-MCBS Working Group. She continues to do her work together with the UMCG oncological staff and PhD student to further implement and improve the EMSO-MCBS.

OncoLifeS (Case study #3)

Understanding cancer heterogeneity, its temporal evolution over time and the outcomes of guided treatment requires accurate data collection in a context of routine clinical care. Therefore, to strengthen and facilitate oncological research in the UMCG, a hospital-based data-biobank for oncology was developed – **OncoLifeS** (*'Oncological Life Study: Living well as a cancer survivor'*). OncoLifeS links routine clinical data with preserved biological specimens and quality-of-life assessments.

OncoLifeS has enrolled more than 5400 patients aged ≥18 years diagnosed with cancer (70% participation rate), representing all major tumor subtypes until the end of 2020. The average age is 63.6±14.2 years and 51.1% are female. In 2014, OncoLifeS started with one tumor board, and gradual extension resulted in the participation of sixteen multidisciplinary tumor boards at present. Besides clinical data (including patient characteristics, treatment details, co-morbidities, lifestyle, radiological and pathological findings), various biomaterials (e.g. blood, tumor tissue) are being collected and stored. Additionally, long-term outcomes and extensive parameters of quality of life are registered, allowing research focused on the long-term adverse effects of treatment and treatment outcomes.

We believe that embedding a data-biobank in clinical care can ensure the collection of high-quality data. Moreover, the inclusion of longitudinal quality of life data enables us to incorporate patients' perspectives, and inclusion of imaging data provides an opportunity to analyze raw imaging data using artificial intelligence (AI) methods, thus adding new dimensions to the collected data[1].

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[1] Sidorenkov G, Nagel J, Meijer C, Duker JJ, Groen HJM, Halmos GB, Oonk MHM, Oostergo RJ, van der Vegt B, Witjes MJH, Nijland M, Havenga K, Maduro JH, Gietema JA, de Bock GH. The OncoLifeS data-biobank for oncology: a comprehensive repository of clinical data, biological samples, and the patient's perspective. Journal of Translational Medicine. 2019, 17:374. doi: 10.1186/s12967-019-2122-x)

Efficacy of COVID vaccination in patients treated for cancer (Case study #4)

It is becoming increasingly clear that the COVID-19 pandemic has a considerable impact on patients with cancer and patient care. The scaled-down capacity to deliver care, fear of visiting hospitals and (the increased) risk of a fatal outcome of COVID-19 infection (due to treatment), have resulted in less patients visiting hospitals and/or strictly adhering to self-isolation, leading to suboptimal cancer care, (additional) mental-health problems and further loss of quality of life.

Meanwhile, several vaccines against COVID-19 were approved. However, often patients with cancer were excluded from the registration trials. Consequently, the efficacy and safety of COVID vaccines for patients with cancer are currently unknown.

Several professional, oncological societies (ASCO, AACR, ESMO and SITC) strongly recommend vaccination of patients with cancer. However, they also emphasize the need for additional evaluation studies on efficacy and safety of vaccines in cancer patients, and how active treatment with chemo- and immunotherapy affects a patient's ability to mount protective immunity against COVID-19 after vaccination.

To tackle this problem, the UMCG[1] initiated the VOICE study[2], a prospective, national, multicenter, longitudinal, multi-cohort study of patients with solid malignancies undergoing active anticancer treatment. From this study, we hope to get more insight into the immunological responses, the longevity of immunity and protection in this vulnerable patient group.

The VOICE study will include 627 patients treated either with chemotherapy (n=246), immunotherapy (n=135) or chemo-/immunotherapy (n=246). Kinetics and strength of the immune response to a COVID vaccine (mRNA) in patients will be directly compared to that of healthy participants (n = 246). Results will reveal how chemotherapy, immunotherapy, or chemo-/immunotherapy influence immune response to COVID vaccination in cancer patient.

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[1] E. de Vries, R. Fehrmann, D. van Baarle, S. Oosting, H. Jalving, in collaboration with colleagues from the ErasmusMC (Rotterdam) and the NKI-AvL (Amsterdam).

[2] VOICE study: 'vaccination against COVID in cancer' (design initiated in August 2020, clinical trial commenced in February 2021); ClinicalTrials.gov identifier, NCT04715438. To maximize usability of our efforts, the clinical study design was published prior to initiation of the study (Nature Medicine, 2021) since it could also serve as a model for translational studies of other vulnerable populations or comparable cohorts vaccinated with different vaccines against COVID-19.