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Editorial

New Chemical Tools for Diagnosis and Treatment of Cancer

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At the biological level, the complexity and diversity of cancer pathogenesis falls within the umbrella of ten hallmarks and four enabling characteristics that have been recently reviewed.[1] Big data sets are being generated in the clinics and by the scientific community to identify, on the one hand, genetic and environmental factors increasing the risks for contracting cancer and, on the other hand, molecular targets and pathways that allow for new diagnosis and treatment modalities. Though overall patient survival has not stopped increasing since the mid-1990s, a great demand still exists toward more effective and more selective methods that can be used in cancer-specific and even patient-specific approaches. Such new approaches, often referred to as "personalized medicine," develop at a fast rhythm by combining the increasing understanding of cancer biology with the atomic precision of modern chemical tools.

This *JACS Au* virtual issue showcases recent striking demonstrations of how new chemical systems and technologies are being developed that can address current challenges in cancer diagnosis and therapy. While many of these reports remain at the fundamental level, they demonstrate that cancer chemical research requires cross-disciplinary approaches, including cell biology, animal studies, and/or clinical sampling.

This selection of articles starts with new methodologies for the diagnosis of specific cancers. For early stage skin cancer diagnosis, an analytical platform based on adhesive sampling and laser desorption ionization mass spectrometry combined with automated interpretation of the results has been shown to be powerful for the detection of skin alterations in a nonsurgical and time-saving manner; 100% accuracy was obtained when the lesions were submillimeter-sized (DOI: 10.1021/jacsau.0c00074). For pancreatic duct adenocarcinoma, which is one of the deadliest cancers due to its propensity for metastasis formation, a successful strategy has been implemented to penetrate the so-called hypopermeable tumors. A nanotheranostic system has been designed with programmable targeting capability; it can cross the barriers of the tumor and map human clinical samples with high resolution, thus allowing early diagnosis by fluorescence measurements (DOI: 10.1021/jacsau.1c00553). New diagnosis tools have also been conceived to improve the performance of the ones currently on the market. In this context, it has been demonstrated that antibody-functionalized 1D and 2D perovskites displaying simultaneous two-photon imaging ability can reveal triple-negative breast cancer cells, making them promising probes for bioimaging applications (DOI: 10.1021/jacsau.0c00038). New bioprobes based on the conjugation of a lanthanide ion and a targeting peptide have been designed with the aim of combining diagnostic and therapy properties. It can selectively bind to a specific target, image it through immunofluorescence, and display a selective cytotoxic effect on the tumor cells (DOI: 10.1021/jacsau.1c00187).

Relevant high-throughput screening platforms are essential tools for the identification of lead compounds that can act as cancer target antagonists. An important class of targets includes transcription factors, which control cell function through protein−protein interactions. A recent "transcription block survival" screening platform was specifically designed as a tag-free genotype-to-phenotype approach to identify therapeutically valuable peptide sequences (DOI: 10.1021/jacsau.2c00105).

Next to imaging and theranostics, considerable effort is also devoted to the development of novel therapeutic approaches, either via searching for new cancer targets, or via the development of new strategies for known targets. In spite of their recognized toxicity, simple metal complexes such as cisplatin have remained effective first-line therapeutic agents used on a daily basis in the clinics. In a constant effort to enlarge the therapeutic applications of transition metal complexes and to improve on the existing platinum anticancer drugs, other metal centers are being actively investigated. Gold-based complexes represent a particularly promising alternative. In spite of the apparently similar electronic configurations of gold(III) and platinum(II), gold(III) complexes show a surprisingly different chemical reactivity, such as "rollover" cyclometalation. The resulting bis-cyclometalated gold(III) complexes demonstrate strong anticancer properties, characterized by a high resistance to intracellular reduction and a 10 times higher cytotoxicity to human cancer cell lines than to noncancerous cell lines (DOI: 10.1021/jacsau.0c00104). Gold(I) complexes can also be prepared that disrupt the mitochondria in cancer cells by severely depolarizing the mitochondrial membrane. Interestingly, their high tolerance in mice tumor models demonstrates undeniable preclinical potential (DOI: 10.1021/jacsau.1c00051). Moving down the d-block toward more oxophilic metal centers, new titanium(IV) complexes have been prepared that display good anticancer properties. They target ribonuclease reductase, an enzyme responsible for the synthesis of ADN bricks.

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Intracellular degradation of the titanium(IV) complex leads both to ligand release, which traps the unbound iron pool necessary for the enzyme activity, and to free Ti^{4+} ion release, which prevents nucleosides from transforming into deoxyribonucleotides (DOI: 10.1021/jacsau.1c00078). Of course, new cancer targets are also addressed using metal-free chemical tools. For example, some growth factor receptors are overexpressed in cancer cells leading to unliganded dimers (i.e., dimers that form in absence of ligand-triggering dimerization). By designing an aptamer that specifically binds to such a growth factor receptor, aberrant receptor dimerization and the signaling processes that follows have been inhibited, which is cytotoxic to cancer cells (DOI: 10.1021/jacsau.0c00121).

Another approach for inducing apoptosis in cancer cells is based on the generation of reactive oxygen species (ROS). Traditional methods use either X-ray or radioactive radiation, as in radiation therapy, or visible light irradiation and a light-absorbing molecule, a technique called photodynamic therapy (PDT). For example, oligothiophenes, which form a well-established compound class extensively used in materials and nanotechnology research, have now been applied for PDT. Their intrinsic hydrophobicity, which in principle makes them poorly biocompatible, has been overcome by bioconjugation to human serum albumin (HAS). Upon irradiation with ultralow light doses, the HAS-oligothiophene bioconjugates effectively produced ROS, which led to eradication of cancer cells at a localized level (DOI: 10.1021/jacsau.1c00061). Next to visible light, new external stimuli are also being investigated for generating ROS. For example, ultrasound has the notorious advantage of penetrating much deeper than visible light into living tissues. Bioinspired hybrid carbon dots have hence been synthesized that allow cell imaging and production of ROS upon ultrasound stimulus, leading to tumor ablation *in vivo* (DOI: 10.1021/jacsau.1c00422).

Instead of changing the type of radiation triggering ROS formation, it is also possible to generate photoactivatable prodrug systems that work via a completely different, ROS-independent mechanism. In the last paper of this virtual issue, Zhang et al. designed systems based on photopolymerization (DOI: 10.1021/jacsau.1c00373). By triggering photoinduced polymerization inside the cells, these systems generate polymers with well-defined structures in living cells, thus inhibiting tumor growth and metastasis both *in vitro* and *in vivo*.

In summary, many chemists have taken up the challenges posed by our improved understanding of cancer biology and pathogenesis, to generate new and exciting tools to fight cancer. These tools often offer increased selectivity and sensitivity due to the combination of new synthetic, computational, and/or analytical methods. At this moment, however, many of these approaches are at an early stage and a long way from the clinics. Of course, new chemistry is always exciting! However, to increase the impact of these new methods, a more "translational" approach may be needed, which demands thorough thinking about the requirements and hurdles of clinical trials and detailed discussions with clinicians. For the benefit of society in general, and of cancer patients in particular, it is important that chemists become more familiar with the essential aspects or current cancer diagnosis and therapy. Translational chemistry deserves to play a key role in chemistry, and it should be considered as early as possible on the road toward new chemical tools for curing cancer. In this context a recent Perspective by Boehnke and Hammond focusing on the nano−bio interface highlighted the need for holistic approaches linking screening and big data approaches to continued development and use of relevant preclinical models (DOI: 10.1021/jacsau.1c00313). New tools emerging at the interface of chemistry, biology, engineering, and medicine will provide exciting possibilities for entirely new therapeutic strategies.

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Notes

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