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From Self-Organization to Tumor-Immune Therapy: How Things Started and How They Evolved

Matthias Barz, Lutz Nuhn,* Gerhard Hörpel, and Rudolf Zentel*

1. Background

On a sunny afternoon in summer 2021, Rudolf Zentel and Lutz Nuhn visited Helmut Ringsdorf in Mainz-Gonsenheim, Germany. It was the first time they were able to meet each other again in person after the long-lasting restrictions of the COVID-19 pandemic. While having a cup of coffee and a slice of cake on the garden terrace, Zentel and Ringsdorf looked back on the early days and "how things started and how they evolved". In a lively discussion the participants shared their thoughts on naïve ideas from the old days, how they continued, evolved and extended in the Zentel lab (**Figure 1**). These ideas were afterwards discussed and co-reflected by former students of the Ringsdorf lab (G. Hörpel, R. Zentel) and the Zentel lab (M. Barz, L.Nuhn). As a result, this perspective article was written, which brings together the individual opinions of the authors as — hopefully — a valuable contribution to *Macromolecular Rapid Communication's* special issue in honor of Rudolf Zentel upon his retirement.

2. Starting Point

The starting point of the work in the Ringsdorf lab was polymer science in the 60s and 70s of the last century (or even better: "the last millennium", quotation by Ringsdorf). At that time, the beginning of the "plastic era" had just started a few decades previously, everything related to polymers was extremely modern, and research on this topic was well supported by chemical industries. Polymers and plastics entered everyday life as commodity products that made life easier in the postwar era. Especially for people who had suffered before from many relinquishments, life became finally more comfortable.

Consequently, polymer science gained much popularity throughout society and received a lot of "freedom and liberty" to explore various non-commercial research niches. From today's point of view, one might claim this golden era of polymers to be the origin of our current problems related to plastic waste pollution in oceans or soils. It is — in this context — however, frankly speaking necessary to consider that these problems are a result of polymers being extremely versatile materials: They have been tailored to fulfil many needs over a prolonged time by very cheap production costs. So, maybe one of their biggest problems is their extremely low price that guaranteed high benefits for the chemical industry, but solidified their status as disposable products. We all know by today that early concepts of recycling and responsible resource and waste management would have been necessary, yet, the overall enthusiasm on the superiority of plastics may have forced these aspects to step aside.

At the same time, life sciences progressed rapidly by a series of new discoveries leading to novel diagnostics and therapeutics, which revolutionized medicine in several fields (e.g., by the support of Rosalind Franklin, James Watson and Francis Crick postulated the molecular structure of DNA in 1953, the same year when Hermann Staudinger was awarded with the Nobel Prize for his discoveries in macromolecular chemistry). A close connection between the – nowadays considered – two worlds of materials and life sciences was still very much existing, especially in the head of Helmut Ringsdorf.

In light of applying polymers in our daily life, typical research topics of polymer science at that time were i) the synthesis of new (in our modern view: rather "simple") monomers and ii) the detailed study of their polymerization, including polymerization kinetics and potential side reactions and thereby obtaining processable materials. Concerning physio–chemical properties, researchers paid further attention on the characterization of polymer viscosity (rheology) in solution and solid-state properties like crystallinity and bulk viscosity. Parallel to this work, new topics evolved to broaden the landscape of polymer applications: i) getting order into "plastics" and ii) getting more (chemical) functionality into polymers to make them useful in completely new areas. And Helmut Ringsdorf was very active in several of these topics.

Concerning the aspect of ordered polymers he was searching for ways to prepare "homogeneously ordered" polymers (in contrast to amorphous or partially crystalline materials). As it was known (at that time) that partial crystallinity resulted from the subsequent crystallization over time, which leaves some parts of the sample in a non-oriented state, he (and others) were searching for the possibility to polymerize monomers in an oriented

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Figure 1. Helmut Ringsdorf and Rudolf Zentel in Mainz-Gonsenheim in summer 2021 (this picture was kindly provided by Lutz Nuhn).

state and to transfer this order into the polymer obtained. But as polymerization in the crystalline state is difficult (e.g., lack of mobility) this required the search for other types of ordered or self-organized systems which combine order and mobility.[1] This led to attempts to polymerize in the liquid crystalline state[2] or in micelles and other amphiphilic structures.[3] And as these approaches were found to be successful, the interest shifted to the study of the resulting ordered polymer structures.[4,5]

Independent of this search for ordered polymers, there was the growing interest in highly functional polymers that enable novel therapies and medical interventions and this was – in some way – a result of the world wars (especially World War II and the subsequent Cold War). Polymeric plasma expanders were studied based on poly(vinylpyrrolidone) (PVP) demonstrating the ability of treating acute injuries of heavily wounded soldiers and civilians.[6] As one of the very first polymer drug conjugates, Horst Jaskewitz then covalently linked mescalin to PVP in the 1950s and observed a prolonged presence of mescaline in the urine of mice.[7,8] These early works supported the findings that some polymers can a) be well tolerated in the body and that they b) differ in their body residence time, since they cannot be as quickly excreted via the kidneys as small molecules.

Based on these considerations and the constant threat of a nuclear apocalypse between the two global powers at that time, Ringsdorf worked for some years on polymers as "long time lasting radical scavengers" to combat γ-radiation from nuclear bomb explosions.[9] He explored long-circulating functional polymers in the blood stream that neutralize ionizing radiation as a robust strategy for helping nuclear victims. After global diplomatic relaxation following the "détente" era of the early 1970s, Ringsdorf continued his interest in polymers for medical applications and developed this aspect further into a promising concept for the treatment of tumors with polymers carrying chemotherapeutics.[10,11] In his conceptual work in 1973 he summarized the idea of conjugating poorly soluble drugs via degradable linkers to water-soluble polymers and further equipping these structures with a homing/targeting unit to achieve a more favorable biodistribution of drugs (**Figure 2**). For this, however, multiple chemical efforts became necessary to fulfil all the requirements for polymeric drug delivery systems, which set the basis for the clinical translation of galactosamine-modified poly(2-hydroxypropyl methacrylamide) (HPMA)-doxorubicin conjugate (PK2) in the following years.[12]

As a result, the research in the Ringsdorf lab in the late 70s and throughout the 80s explored various aspects of "polymers for tumor therapy"[11,14] as well as on "self-organized systems"[1] including LC-phases, lipid layers and liposomes (**Figure 3**). Such systems, which combine "order and mobility", could nicely be addressed after a systematic route to LC-side chain polymers was established in 1978.[15] This work was later summarized by Wüstefeld, Zentel et al.[1] Further work in this field also included curious findings like the "Wheel of Mainz".[4] On the other side the aspect of polymer drug conjugates[14] and liposomes (as well as other membrane models)[16] overlapped more and more. All these research lines and their interplay inspired Rudolf Zentel, who worked in the Ringsdorf lab at that time, beyond all measures.

3. How was life in the Ringsdorf lab?

As a scientist, Ringsdorf's greatest ability was to think differently, identify new concepts and encourage people from different

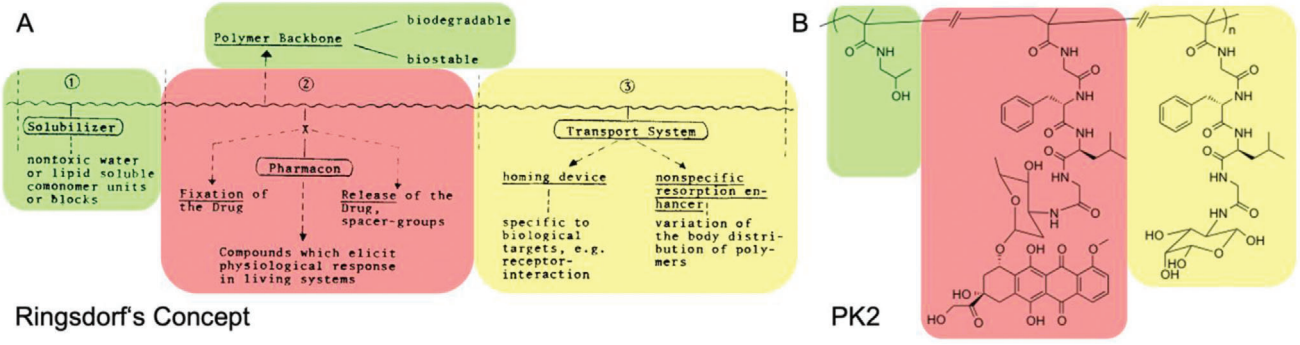

Figure 2. A) Helmut Ringsdorf's concept of pharmacologically active polymers. A water-soluble and biocompatible polymer backbone (green) carries bioactive drug through a cleavable spacer (red) and a cell-specific targeting group (yellow).[11] B) Following this concept the galactosamine-modified HPMA- doxorubicin conjugate PK2 was developed and tested in first clinical trials[12] (all required features are highlighted in green, red, and yellow). Reproduced with permission.[13] Copyright 2014, Wiley-VCH GmbH.

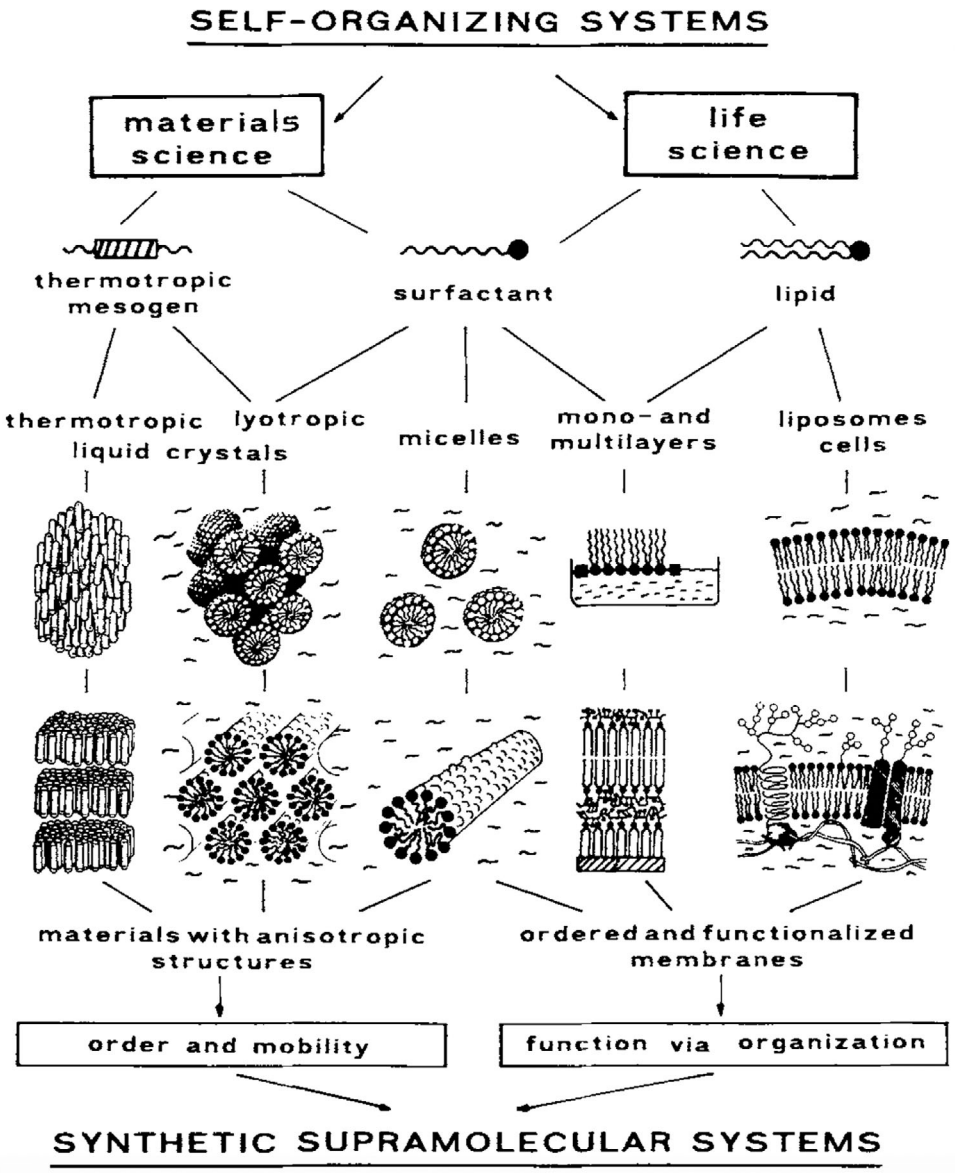

Figure 3. Materials science and life science of the Ringsdorf lab were influenced by self-organization and supramolecular systems ranging from thermotropic liquid crystals to liposomes. Reproduced with permission.[16] Copyright 1988, Wiley-VCH GmbH.

disciplines to work together on new interdisciplinary topics. A question behind it remains: How did he bring necessary new information together?

This would not have been possible without his many national and international contacts and without his uniquely open personality. He did not take science – and his personal understanding of science – too serious. This allowed him to live with many aspects of "half-knowledge" (quotation by H. Ringsdorf) and partial understanding of facts, basing his decision mostly on how much he trusted a person in the discussion. In addition, he did not "weigh the arguments" by the hierarchical position of his counterpart, whether they be a well-known professor or a young student. In addition, he stressed – during discussions in the group – that there are "nearly-no real stupid questions", but that many ideas, which sound strange at first (H. Ringsdorf called them "*Schnappsideen*") can sometimes turn into something great. By such statements, he acted not like typically professor, because often other professors of that time liked to be the expert on a distinct research area. This thinking, however, limited their investigations only on topics they were familiar with.

The "reaction beaker" where this concept worked well was his group and the associated scientists. And they were "carefully selected". Simply more on their ability to act independently than by always looking for the very best grades or the reputation of the group. As a result, his students spontaneously organized themselves in their research and in their lives in much the same way as the themes of Ringsdorf's research on the topics of "liquid crystals" and "lipid membranes".[1,16]

Regarding polymer therapeutics, the group started to differentiate between two strategies to attack cancer either on a "cellular" or on a "molecular" (pharmaceutical) level.[14,17] While the first one was very much inspired by the lessons learnt from stabilizing lipid membranes and, thus, theoretically generating synthetic containers which could in principle act as artificial cytotoxic cells to eliminate tumor cells (in analogy to immune cells), the second strategy focused on cytotoxic polymer-drug conjugates and how such systems can access tumor cells, get internalized and release their drug inside the cell. Thereby, first considerations were made on how polymer-drug conjugates can safely be administered, get to interact with the tumor cell surface, induce endocytosis and lysosomal drug release from a so-called lysosomotropic carrier (according to Christian De Duve[18]). Improved drug design was further focused on polymer-mediated depot effects (to reduce the frequency of application) and detoxification (while maintaining the therapeutic effects and increase selectivity).

As an example, the active pharmaceutical ingredient (API) cyclophosphamide is approved for the treatment of cancers of the bone marrow (leukemia, "blood cancer"), lymphatic system, breast, ovaries, lungs, bones, and central nervous system. However, treatment with the free drug caused severe adverse effects such as nausea, vomiting, dizziness and visual disturbances, possibly leading to circulatory weakness. As bad as the side effects are for the patients, they were the ideal motivation for testing the model of detoxification of polymeric antitumor agents. First, cyclophosphamide-methacrylate monomers were copolymerized with water-soluble monomers to obtain polymer drug-conjugates. These initial systems, however, suffered from a loss of anticancer activity due to the way of drug conjugation.[19]

It may be considered fortunate that Brock et al. had previously found,[20] in the context of studies on the mechanism of action, that in vivo the activated cyclophosphamide was formed by microsomal hydroxylases, but that it immediately decomposed into the de-alkylated derivatives. It was also fortunate that the activated cyclophosphamide was synthetically accessible via an oxidation reaction described by Peter and Hohorst.[21] Following the biochemical reaction of activated cyclophosphamide with SH group-containing proteins, spacer molecules were synthesized by Klesse et al[22–25] and reacted with the activated cyclophosphamide. The conjugate molecules were considered to cleave at the sulfur bond in the cell and release the activated cyclophosphamide to exert the therapeutic effects. It could be demonstrated that the cleavage of the sulfur bond is ruled by both the hydrophobic/hydrophilic balance and the steric hindrance of the spacer molecule.[22] In other words, these findings underline that APIs can be linked to polymers by cleavable spacers.

For the validation of the conjugates with respect to their therapeutic effect Helmut Ringsdorf realized multiple cooperation with cancer research labs worldwide. Several investigations were conducted at the National Cancer Institute (NCI) at NIH/Bethesda, where the DNA crosslinking potential of the cyclophosphamide-spacer conjugates was identified successfully. Interestingly the conjugates even showed a slightly improved therapeutic efficacy in tumor-bearing mice than the soluble cyclophosphamide.[26]

Back in the chemical Ringsdorf lab in Mainz, these encouraging results led to the fixation of various other drugs to polymer backbones. To gain access to such highly functional polymers chemically, the group explored various types of polymers as carriers. Beyond PVP that was used in the very first polymer-drug conjugate studies,[7,8] poly(ethylene glycol) (PEG) raised attention for several parenterally well-tolerated applications.[27,28] However, PEG only allowed modifications of the end groups to introduce pharmacologically active compounds, thus, other functionizable polymers seemed to be required. In that respect, the Ringsdorf lab already identified precursor polymers as valuable tool to introduce drugs in a flexible matter by post-polymerization modifications.[29] Among them, the reactive ester chemistry[30] was recognized as versatile opportunity to address the needs of reliable polymer drug conjugation. Poly(methacrylate esters) of *N*-hydroxysuccinimide (NHS), *N*-hydroxybenzotriazole (HOBt) and 2,4,5-trichlorophenol could be converted into functional water-soluble polyamides by quantitative aminolysis, thus, providing access to various types of pharmaceutically active polymers.[10,31]

At the same time, Jindřich Kopeček and co-workers established *N*-(2-hydroxypropyl) methacrylamide (HPMA) copolymers[32,33] as water-soluble polymers with low immunogenicity and toxicity.[34,35] These polymers were accessible by simple radical polymerization strategies. In close interaction, the Ringsdorf lab also applied these polymers to attach drugs or drug-spacer systems via esterification. In order to maintain water solubility, they found that a conversion of 10–15% of OH-groups should not be exceeded. Alternatively, HPMA-doxorubicine conjugates showed also most promising results in the Ringsdorf lab when a pH-degradable hydrazone spacer was chosen.[17,36] The Kopeček group further established HPMA-based doxorubicine drug conjugates with cathepsin-degradable linkers. Successful candidates were developed within 25 years to finally enter clinical trials for

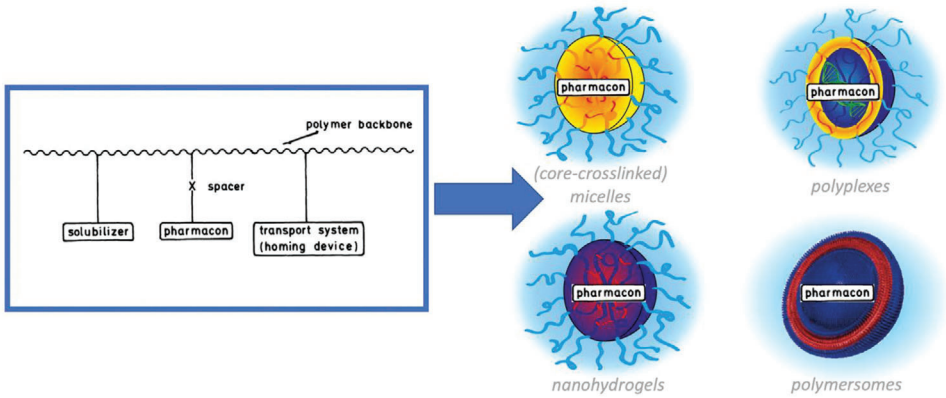

Figure 4. "Extended Ringsdorf-Model" which includes a topolocical information for the drug carrier to shield the drug from degradation or premature recognition by using, e.g., (core-crosslinked) polymeric micelles, polyplexes (for RNA/DNA delivery), nanohydrogels and polymersomes (the picture on the left was taken from the Gerhard Hörpel's Ph.D. thesis; [22] the cartoons on the right were reproduced with permission.[50] Copyright 2013, Springer Nature).

cancer therapies.[37] Primarily supported by comprehensive work of Ruth Duncan, a frequent guest in the Ringsdorf lab and still a close friend to the Ringsdorf family as well as an honorary Ph.D. of the University of Mainz, [38–40] a lot of efforts were made in the HPMA-doxorubicin polymer conjugate PK1[41] becoming the first passively tumor-targeted polymeric prodrug which was intravenously injected into cancer patients in 1994.[42] A few years later, the galactosamine-modified HPMA-doxorubicin conjugate PK2[12] as actively targeting polymer-drug conjugate following the Ringsdorf model (Figure 2) was evaluated in patients with primary or metastatic liver cancers. From today's point of view, these pioneer studies generated a better understanding of polymer therapeutics in a biologically complex environment and how to improve cancer therapy.[43]

The Ringsdorf lab at the time also investigated other water-soluble polymers equipped with drug-spacer including divinyl ether-maleic anhydride (DIVEMA) copolymers, polymeric dextrans, and poly(ethylene imine) (PEI), however, with lower biocompatibility compared to PHPMA. Interestingly, all drug-polymers showed a much higher cleavage rate than the corresponding drug-spacer-conjugates itself. Though, at least the dextran drug had a much lower toxicity and thus allowed a higher maximal tolerated dose (MTD), but researchers worried that the release of, e.g., cyclophosphamide may already occur during transport through the bloodstream and not only at the tumor or in the tumor cell. This was the moment when the Ringsdorf model had to be extended.

In analogy to lipoproteins, self-assembling micellar polymer structures were synthesized, which allowed to protected the drug inside the core of micelles, somehow like a Trojan horse.[22] The polymeric micelles were realized by using various polymers. One of the most promising systems was a drug containing block copolymer polymeric micelle according to **Figure 4**. The hydrophilic block consists of a polyethylene oxide, which was connected to a hydrophobic block containing the drug linked via a cleavable spacer to a poly-L-lysine block (PLL). The PLL was considered to be degraded after transport, which should minimize long term adverse effects, e.g. storage diseases.[22] In summary, the following picture emerged: [22] While PLL itself was markedly toxic to cells, the polymeric antitumor agent with the modified PLL in the inner hydrophobic block showed no toxic effect at all applied concentrations. Moreover, the death curves of L1210-tumor bearing mice were striking: the polymeric antitumor agent contributed to a significant prolongation of life despite a low dose calculated on the cyclophosphamide fraction.[22]

Most importantly, this concept of PEG-block-poly(amino acids) was applied and greatly extended by the group of Kazunori Kataoka and led to 4 systems in clinical evaluation, which clearly underlines the enormous potential of block copolymers as relevant and translatable nanomedicine.[44–49]

As a last note from these early days, one should highlight that the role of the immune system in the context of tumor was already discussed by H. Ringsdorf and his colleagues, too.[17] Beyond the immunoadjuvant properties that were investigated for methotrexate containing divinyl ether-maleic anhydride (DIVEMA) copolymers on tumor-associated macrophages,[51,52] concepts to stimulate immune cells, address tumor-associated antigens or mimick cancer-specific cytotoxic T-cells were considered, which are nowadays becoming a valuable tool for polymer-based immunodrug delivery systems to improve cancer immunotherapy. Interestingly, these concepts inspired Rudolf Zentel and colleagues nearly 20 years later as starting point to initiate a collaborative research center (CRC/SFB 1066) exploring tumor immune therapies via the help of nano-sized polymeric materials.[53–56]

4. How did this inspire Rudolf Zentel and next generations?

Rudolf Zentel did his diploma, his Ph.D. thesis and – after a year as a postdoc in Freiburg – his habilitation in the environment of the Ringsdorf lab. He started his diploma thesis in November 1978 with work on liquid crystalline polymers.[57] During his Ph.D. at the border of synthetic polymer science and polymer physics[58] (his thesis was jointly co-supervised by H. Ringsdorf and the polymer physicist G. Strobl) he focused on structure–property relations in "self-organized systems", mostly liquid crystals, and he continued to work in this context for his habilitation from 1985 to 1989[59,60] whereby he then focused more and more

Figure 5. Rudolf Zentel as habilitand with his mentor Helmut Ringsdorf in 1985 (picture was kindly provided by Rudolf Zentel).

on LC-elastomers as recently summarized here.[61] He selected this facet, where order plays a major role, because the cooperation between synthetic chemists and material scientists to combine synthesis and physico-chemical characterization was well established in Mainz, while it was rather challenging to find support for proper biomedical characterization of relevant samples. And as a young man (compared to H. Ringsdorf) he liked to have his own scientific topic "under control" and with less uncertainties (**Figure 5**).

But apart from the selection of his own area of research, he was also strongly involved in the discussions on polymers for biomedical applications (**Figure 6**) and H. Ringsdorf still insists that "he [Rudolf Zentel] prepared some of the best lectures on pharmaceutically active polymers during the so-called Hütten-Seminars [group seminars]". That may stem from the fact that he had chosen biochemistry as additional topic during his chemistry studies. Consequently – on the other side – he had to get trained in "polymer chemistry" later during his Ph.D. thesis, when he acted as teaching assistant during courses in polymer science.

Later on (after 2005, when he was now a full professor in Mainz, and "older") Rudolf Zentel started again – in some type of "homecoming" – to work on polymers as drug carriers. This shift was initiated by i) growing interest in the department on this topic and the ii) recognition of the potential of the newly established reactive ester monomers,[62] which had just been established by Patrick Theato in his group. With their help functional biocompatible block copolymers could now be polymerized in a well-controlled way via RAFT polymerization by a talented Ph.D. student, namely Matthias Barz, giving access to block copolymers and to well defined nano-structured entities (polymer micelles, as well as later on also core-crosslinked micelles and polymersomes, see Figure 4), as summarized here.[13] Most

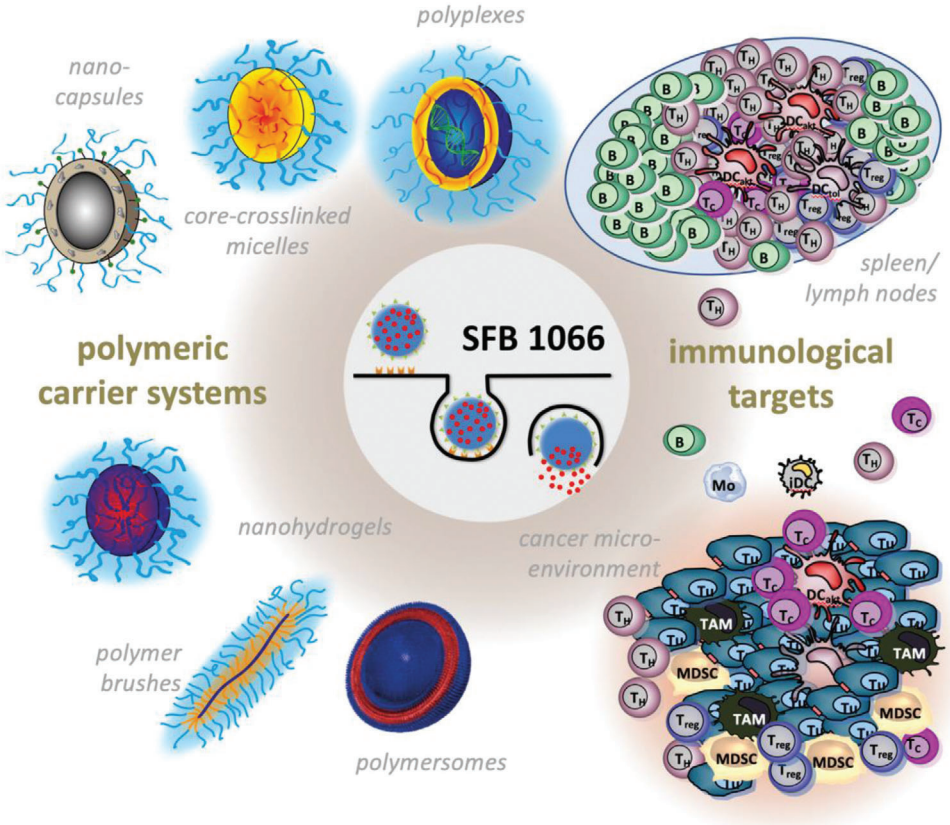

Figure 6. Polymeric carrier systems and immunological targets currently explored by the collaborative research center CRC/SFB 1066 (the cartoons on the left were reproduced with permission.[50] Copyright 2013, Springer Nature. The cartoons on the right were kindly provided by the CRC/SFB 1066).

importantly, the polypentafluorophenyl (meth)acrylate polymers enabled the synthesis of reactive (block) copolymers with the hydrophobic lauryl methacrylate, which could be easily converted into (multi)functional amphiphilic pHPMA copolymers.[63] This pathway avoided simple problems like finding a common solvent for pHPMA based amphiphiles for characterization, while the conversion under controlled conditions can prevent undesired side reactions, such as reactive ester hydrolysis.[64] In addition, the establishment of a cooperation with Frank Rösch at the Insitute of Nuclear Chemistry facilitated the use of positron emission tomography (PET) to study the body distribution of the newly prepared nanoobjects directly and, thus, to get a direct feed-back between molecular and supramolecular structures and their body distribution.[65,66] Matthias Herth and Matthias Barz established together the first ^{18}F-labeling of polymers, which made it finally possible to identify better in vivo structure-property relations.[65]

In addition, the link to immunology at the University Medical Center in Mainz made it possible to interact closely with biomedical researchers focusing on the immune system as therapeutic target. The immune system thereby gained more attraction because of two reasons: First, cancer-immune therapy requires a strong and selective activation of the immune system (that means enough cells of the immune system, but not all must be reached). It does not require the direct killing of all tumor cells by the applied drug, since this will be done (in a more professional way) by the body´s own immune system.[52] Secondly, the immune system is well addressable with nanostructures as nicely demonstrated by another extraordinary Ph.D. student in the Zentel lab, namely Lutz Nuhn.[53,67] He applied the reactive ester approach to access HPMA-based block copolymers and utilized them to generate more complex polymer conjugates. For instance, the amine-selectivity of the PFPMA-block allowed him to install glycopeptides of cancer associated MUC1-derived antigens established by Horst Kunz, Sebastian Hartmann and coworkers together with orthogonally addressable alkyne entities onto HPMA home and block copolymers.[68] By further conjugation of T-helper cell epitopes, these structures were applied as anticancer vaccines and interestingly, the polymers containing self-assembling lauryl methacrylate block domains yielded highest antibody titers against the tumor associated MUC1, probably due to the multivalent presentation of the antigen to the immune cells during vaccination.

Now, with his background from the Ringsdorf lab, Zentel was very much familiar with the origins of applying polymer drug carriers into the body. Moreover, he had already experienced that it is well possible to work on very different interdisciplinary topics simultaneously. Still, it was quiet a move because at the same time he was well established in the field of materials science (mostly liquid crystals,[1,57–60,69–71] but also helical polymers[72] and polymer opals, [73] see[61] for a collection). In addition he was the German speaker of an "International Research Training Group" (IRTG 1404) with South Korea, dealing with OLED materials.[74–76] Nevertheless, all these activities motivated him to found together with Katharina Landfester and Stephan Grabbe the first CRC on nanomedicine and nanoparticle-based tumor immune therapy in Germany (SFB 1066) containing expertise from 50% chemistry and 50% biomedicine leading to novel polymeric nanoparticles that are effective for cancer immunotherapy (Figure 6).[53–56]

But this required again – besides the established scientists willing to set the frame – young people, who started to work on this topic and continue to push it forward. The two former Ph.D. students of Rudolf Zentel, Matthias Barz and Lutz Nuhn, may serve as examples who experienced the "Ringsdorf-Zentel lab spirit" shaping their independent research careers at the interface of polymer science, pharmaceutical sciences and medicine.

After postdoctoral research stays in the labs of Maria J. Vicent (Valencia, Spain) and Tomas Kirchhausen (Harvard Medical School, Boston, USA) Matthias Barz established a junior research group in Mainz in 2013. During his habilitation period, he worked on polypept(o)ides, (combinations of a functional/reactive polypeptides with polysarcosine).[77,78] He developed S-alkylsulfonylcysteine and -homocysteines that are applicable for peptide synthesis by classical peptide coupling and N-carboxyanhydride polymerization. Afterwards the S-alkylsulfonyl protective group can be reacted with thiols yielding unsymmetric disulfides for chemoselective bioconjugation or bioreversible cross-linking chemistry.[79–82] Based on this chemical tool box Matthias Barz synthesized core-crosslinked polymeric micelles,[79,83–85] polymersomes,[86] nanohydrogels and polyplexes, [87] lipid nanoparticles,[88] molecular polymer brushes[89–91] and organic-inorganic hybrid systems.[89–91] In line with Rudolf Zentel's vision that every system shall be designed to fulfil a rational need, Matthias Barz's systems enable therapeutic interventions, e.g., in cancer diagnosis[89] and therapy,[92] (immune) therapy[91,93,94] and bacterial infections.[95–97] With polysarcosine[77] as hydrophilic, stealth-like polymer material (as relevant substitute to PEG[91,98–100] with an improved immunogenicity profile[88,101]) multiple biomedical research projects have been initiated by him that are also applicable to large scale GMP production.

The other young researcher continuing biomedical research on a highly interdisciplinary level is Lutz Nuhn. After an exchange semester in the lab of Bob Langer ("catalyzed" by Helmut Ringsdorf),[102] he started his diploma and Ph.D. work in the group of Rudolf Zentel. Lutz Nuhn focused on the development of nanohydrogels with cationic cores.[103] He found that amphiphilic block polymers based on pentafluorophenyl esters can already undergo self-assembly in polar organic solvents.[104] The obtained precursor micelles can be cross-linked in a controlled way by aminolysis and thus chemically converted into functional nanohydrogels. This approach promoted the delivery of sensitive biomolecules including gene modulating siRNA oligonucleotides [55,105–109] or immunostimulatory CpG oligonucleotides.[110] Due to their lymphatic accumulation after subcutaneous injection, Lutz Nuhn applied pH-degradable nanohydrogels[111] during his postdoctoral time with Bruno De Geest (Ghent Unversity, Belgium) for the delivery of covalently attached immunostimulatory cues for vaccination and local cancer immunotherapy.[112–115] Alternatively, surface decoration with advanced targeting units (e.g., nanobodies)[56,116] addressed and repolarized tumor-associated macrophages.[117] After joining Tanja Weil's department at the Max Planck Institute for Polymer Research and establishing his independent research group in 2019, he continued on immune modulating polymer-based nanocarriers.[115,118] He recently demonstrated that the reactive precursor approach is also applicable to other polymer backbones[119] and alternatively, other amine reactive

entities like squaric ester amides provide access to systemically injectable immune modulatory nanohydrogels (so-called squarogels). [120] Additionally, pH- and reductive responsive delivery systems have been introduced to trigger the on-demand immunodrug release and controlled carrier degradation more precisely.[121,122]

The rapid progress of both junior scientists as well as many other researchers in Mainz is for sure related to the biomedical research infrastructure related to CRC 1066, and thus a continuity of the "Ringsdorf-Zentel lab spirit".

5. Outlook

Having covered only a fraction of ongoing interdisciplinary polymer research in Mainz (and there is a lot more), the question remains what is next to come. Here, the authors, and in particular the honored of this special issue, Rudolf Zentel, would like to provide their view on the future of interdisciplinary research especially in the area of polymer-based nanomedicines:

A first polymer-science related point is the biodegradability of materials, which is currently discussed extensively for commodity polymers to prevent pollution. However, this seems to be from the point of view of all authors a general prerequisite for most in vivo applications. To avoid storage diseases and minimize the exposure of polymeric materials to our immune system we do feel that (on demand) biodegradable systems are highly desirable to avoid total dependency of renal or hepatobiliary excretion. However, we are all well aware that certain properties, such as a stealth-like nature of nanocarrier surfaces needs to be preserved for several systemic applications. The latter affords the need of biodegradable PEG alternatives, which can either be based on synthetic or natural polymers. Polysarcosine may be such a material, but needs to prove its potential in clinical studies.

The same aspects discussed for polymers hold also true for functional systems constructed thereof. Micelles, polymersomes, nanohydrogels, polyplexes, liposomes and lipid formulations all need to provide stability for a certain time from the cargo's point of view to protect it from degradation, premature systemic release or rapid excretion and at the same time guarantee its efficient delivery as active pharmaceutical ingredients to its side of action. After having fulfilled these challenging tasks, the nanoparticle carrier needs to fall apart, ideally into non-toxic metabolites, and disappear.

In the tradition of the Ringsdorf and Zentel labs, facile (macromolecular) chemistry and support by an interdisciplinary research environment are both needed to address these requirements. The spirit of the Ringsdorf-Zentel lab may therefore hopefully still stimulate further polymer chemists to contribute to next generation of nanosized drug carriers.

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Conflict of Interest

The authors declare no conflict of interest.

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