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The “Carbonyl Story” and Beyond; Experiences, Lessons and Implications

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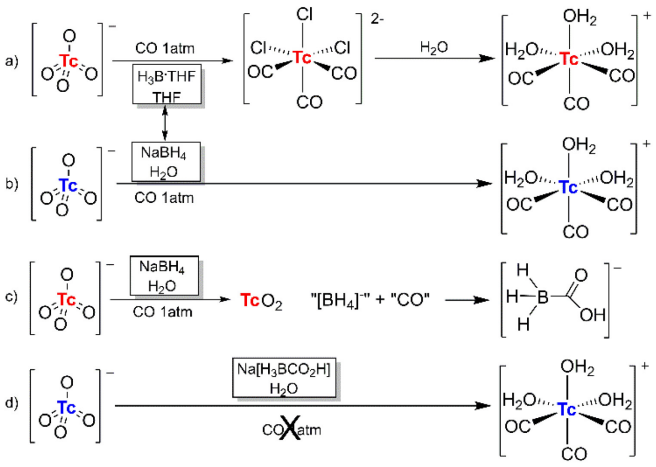
Abstract: The complex $[^{99m}Tc(OH_2)_3(CO)_3]^+$ has become a versatile building block in radiopharmaceutical chemistry, applied by many groups worldwide. Despite many efforts, only one compound made it finally through clinical trials. Along the way from its discovery to the development into an eventual product, the author experienced issues that he would handle differently in retrospect. These experiences are turned into “lessons” in this article that might be helpful for young researchers finding themselves in similar situations. Beside issues with patenting and company strategies, the carbonyl story provided scientific implications beyond the carbonyl story, and insights from which any future ^{99m}Tc-based chemistry for radiopharmacy or molecular imaging might benefit.

Carbon monoxide (CO) complexes are not a class of compounds one would immediately relate to imaging agents with short-lived radionuclides such as ^{99m}Tc ($t_{1/2}$=6h). Typically prepared at high pressure-high temperature conditions and in organic solvents, their syntheses seem to contradict any preparative requirements for routine application in hospitals. Indeed, such CO complexes were not supposed to find any application in the beginning, when the main question was about how to prepare complexes with the *fac*-$[^{99}Tc(CO)_3]^+$ core at ambient CO pressure. The question arose from the chase to the still elusive complex $[Cp^*{}^{99}TcO_3]$, a homologue of the well-known $[Cp^*ReO_3]$ ($Cp^*=[C_5Me_5]^-$).[1] $[^{99}Tc_2(CO)_{10}]$ was prepared by an adapted rhenium synthesis[2] under medium-high pressure conditions at Los Alamos National Laboratory in the group of Prof. Al Sattelberger. This method could though not be pursued in our labs since reactions in autoclaves with radioactive materials were not allowed. The other medium CO pressure synthesis by Knight et al. to $Tc_2(CO)_{10}$ was also not appropriate for the same reasons.[3] Challenged by the fundamental question to prepare *fac*-$[^{99}Tc(CO)_3]^+$-type complexes at ambient CO pressure, we bypassed $^{99}Tc_2(CO)_{10}$ and found a direct path to $[^{99}TcCl_3(CO)_3]^{2-}$ directly from $[^{99}TcO_4]^-$ or $[^{99}TcOCl_4]^-$.[4] Subjecting many reductants to the reaction of $[^{99}TcO_4]^-$ to carbonyls, borane $H_3B{\cdot}THF$ turned out to be the reductant of choice. This purely fundamental ^{99}Tc chemistry did not imply its use in radioimaging agents at all. This vista turned when we stated excellent water solubility and stability of $[^{99}TcCl_3(CO)_3]^{2-}$ or whatever formed from it in solution. We identified this compound as $[^{99}Tc(OH_2)_3(CO)_3]^+$, an organometallic semi-aqua-ion, as we termed it. Educated in the spirit of "no water - no air" in organometallic chemistry we learned in **lesson 1** that organometallic compounds subjected to water may reveal unintended and surprising features. Precedence for complexes of the type $[Ru(\eta^6\text{-}C_6H_6)(OH_2)_3]^{2+}$ and others were described in the literature but they were rather considered as exotics at that time.[5] Since then, the field of bioorganometallic chemistry, organometallic complexes in biological environments, experienced an incredibly rapid growth.[6]

Far away from our original intentions, $[^{99}Tc(OH_2)_3(CO)_3]^+$ and its rhenium homologue revealed an extremely rich and biocompatible coordination and organometallic chemistry in water.[7] It coordinated essentially to all type of donors, thereby forming highly robust but yet flexible complexes. Being very enthusiastic about these features, we presented the results (with ^{99}Tc and Re) to our then industrial partners, Mallinckrodt Med. B.V., Petten NL. They liked the perspectives (and the chemistry) but asked about an aqueous preparation, compatible with demands from routine preparation and, of course, with ^{99m}Tc. Carbonyl complexes from water (not from concentrated acids) are a challenge but finally the preparation with $[BH_4]^-$ and an atmosphere of CO gave very satisfying results. This synthesis is still done nowadays where boranocarbonate (vide infra) is not available.[8] **Lesson 2**: Fundamental chemistry inspires applied chemistry.



Scheme 1. Discovery and development; the organometallic synthesis with ^{99}Tc (a), transfer to ^{99m}Tc in water, gaseous CO unsuitable for routine production (b), identical reaction with ^{99}Tc gives only $^{99}TcO_2$ and combining $[BH_4]^-$ with unsuitable CO(g) leads to boranocarbonate (c) and the final, suitable production of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ in the Isolink® kit by Mallinckrodt Med. B.V. Knowing from a) that $[^{99}Tc(OH_2)_3(CO)_3]^+$ is a stable and very versatile building block made the development worthwhile.

The aqueous synthesis of $[^{99m}Tc(OH_2)_3(CO)_3]^+$ was well received by the partners at Mallinckrodt B.V., but entailed the question "can you do it without CO?" Slightly puzzled by this question we asked

back "… and without technetium as well?" Finally understanding what they meant - CO is a toxic gas and cannot be handled in production on a routine base – induced the search for a stable compound that would release CO from water under more or less neutral conditions. There are not many of those, if ever, but the old literature revealed boranocarbonate.[9] Boranocarbonate is based on the CO adduct of BH_3, H_3B-CO. The CO is bound to BH_3 by σ-donation only, which shifts its ν_{CO} band to wavenumbers higher than the ones of free CO. Under alkaline conditions, hydroxide attacks the highly electrophilic carbon in H_3B-CO and forms the corresponding carboxylic acid $[H_3B\text{-}COOH]^-$(Scheme 1), comparable to what is found in many metalacarboxylic acid-type complexes

$Na[H_3B\text{-}COOH]$ is a wonderful and small compound which fulfils all requirements, it is water soluble and stable at pH>7 but releases CO at elevated temperature or at low pH. The same time, the "BH_3" unit serves as a reductant like $[BH_4]^-$ did this before. The reaction of boranocarbonate with $[^{99m}TcO_4]^-$ gave $[^{99m}Tc(OH_2)_3(CO)_3]^+$, after numerous optimization trials in quantitative yields. Its aqueous stability enabled lyophilisation and therefore kit preparation.[10] **Lesson 3:** applied questions from industry as confusing as they may be, induce fundamental research.

R&D and especially Dr. Hector Knight at Mallinckrodt was very enthusiastic and supportive. He pushed the project and patenting in particular from then on. Mallinckrodt Med. B.V. prepared kits, the so-called Isolink® Kit, which were distributed for free all over the world. Paul Scherrer Institute and the University of Zurich issued an exclusive license on the carbonyl technology to Mallinckrodt Med. B.V, which ultimately turned out to be disadvantageous. At that time, a controversy article about the carbonyl technology "*$[Tc(CO)_3]^+$ Chemistry: a Promising New Concept for SPET?*" was published by the Eur. J. Nucl. Med. Mol. I., the author taking the pro and Dr. Michael Welch the contra arguments.[11] This authors arguments were mainly chemically based, e.g. "*Thus, the complex $[^{99m}Tc(OH_2)_3(CO)_3]^+$ has mutated from an "exotic organometallic moiety with toxic ligands" to a serious, routinely available compound*" whereas Welch agreed on the chemistry but asked "*Why are there no $[Tc(CO)_3]^+$ labelled agents in clinical trials?*". His answer "*… it does not appear as if Mallinckrodt (now Tyco Healthcare) are actively pursuing new radiopharmaceuticals based on the $[M(CO)_3]^+$ moiety." This apparent lack of interest by the patent assignee is one of the major reasons why radiopharmaceuticals utilizing this interesting functional group are not in clinical studies*." We dissented this argument but on the long run, it turned out to be true and being one of the reasons why almost no radiopharmaceutical with this technology was or is in clinical trials or even on the market. Since we licensed exclusively, there was no way to involve competitors. **Lesson 4**: never license a generally applicable technology exclusively; it will be out of your hands.

Mallinckrodt Med. B.V. (and our patents) was taken over in the same year by Tyco Health Care, a company that had not much to do with radiopharmaceuticals. A few years later, Mallinckrodt Med. B.V., now in Tyco Health Care, was acquired by Covidien Pharmaceuticals, USA. All these company transfers (for a full list see https://en.wikipedia.org/wiki/Covidien) disfavored any targeted development of the carbonyl technology towards a product due to the exclusive licenses that went along with these acquirements. In 2012 finally, the exclusive license could be suspended and a sublicense was issued to Molecular Insight Pharmaceuticals Inc. (MIP). MIP started to develop a prostate imaging agent with the carbonyl technology and the compound MIP-1404 was pursued with engagement. Soon after, MIP was close to bankruptcy and was acquired as a whole in 2013 together with those patents still being actively pursued by Progenics Pharmaceuticals Inc. They pushed MIP-1404, enrolled it into phase I-III clinical trials and considered it as one of the most advanced assets in the Company's pipeline of PSMA targeted diagnostic imaging agents. In 2019, Progenics and ROTOP Pharmaka GmbH, Dresden Germany, announced an exclusive agreement under which ROTOP agreed to develop and commercialize MIP-1404 in Europe, about three years before the decisive patents would expire. **Lesson 5**: Stay in good mood even when you cannot follow the company's strategies and your invention is out of sight.

Throughout these numerous changes and transfers, it is of highest importance to be backed up by professional offices like the University of Zurich has with Unitectra Technology Transfer, this is l**esson 6**. All the legal documents as related to patenting, licensing, sublicensing, research contracts, memoranda of understanding, confidentiality agreements and so forth and the survey that they are followed by the company will otherwise not leave you a free minute.

Despite this rather cumbersome series of events, we were continuously financially supported by the respective companies, not only with license maintenance fees but also with research funds, which we negotiated along with the license contracts. It is an opportunity to negotiate such research funds. For what they are used must not be directly defined by the industrial partner but it has the right e.g. to patent the outcome if interested before it is published. In the carbonyl technology, this was a very beneficial architecture together with Mallinckrodt Med. B.V., which allowed us to explore freely fundamentals for and eventual use in ^{99m}Tc imaging. According to the contract, Mallinckrodt issued about ten patents as an outcome of this supported research for which it also was assigned as the exclusive licensee (!). **Lesson 7**: Combine technology transfer to a company if possible with accompanying research funds.

Finally yet importantly, the ownership of the patents was an issue in the beginning of the carbonyl technology. As **Lesson 8**, it is most important (and now commonly practiced) that the academic institution, where the invention has been made, is the owner of the patent. By licensing to a company, the partner takes over the considerable, number of countries-dependent, patent maintenance fee, which can hardly be afforded by most academic institutions but the institution owns still the patent.

Rewards from the patent in form of license fees or, in an ideal case, from royalties, are generally divided according to the rules of the institution. At UZH for instance, the policy is that rewards from royalties and other fees are equally divided between the university, the research group and the inventor(s), one third each.

As a conclusion, if you as a research group discover or invent something that might be of commercial interest, a patent application is launched. Ideally, this happens already at this stage together with a company. During the following priority year, related fees are affordable. If not already available, as was the case of the carbonyl technology, an industrial partner must be sought during this period. If no partner is found, it is in most cases

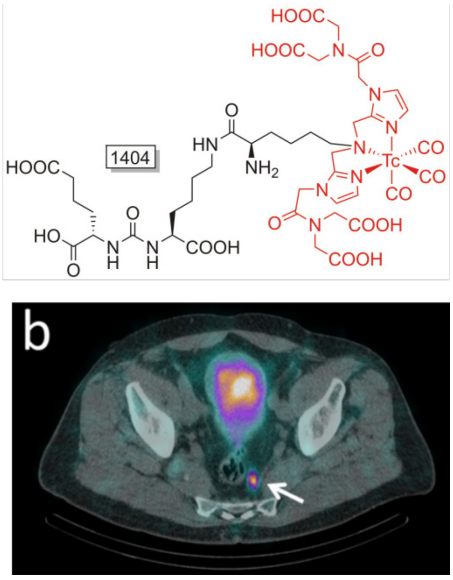
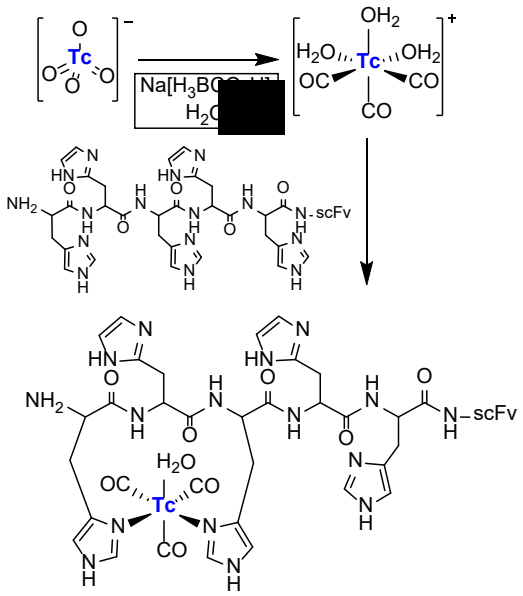


Figure 1. The structure of the PSMA imaging agent MIP-1404 (a)[12] and SPECT/CT fusion imaging showing MIP-1404 positive lymph node metastasis (b)[12b, 13] (credits to Rotop Pharmaka GmbH and Prof. C. Schmidkonz, Erlangen, for providing this image).

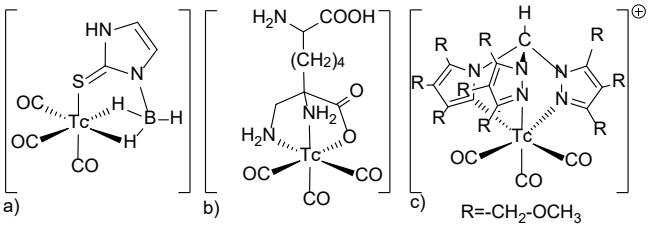


Scheme 2. Direct labelling of his-tagged scFv, a convenient method of labelling recombinant proteins without the need for a bifunctional chelator.

redundant to pursue the application. This applies especially to the medicinal field, where the time span from bench to bedside is typically very long. In our case, it took about eighteen years from the invention until the only product MIP-1404 finished phase III clinical trials but this was clearly not due to missing opportunities. Why did the carbonyl technology not produce more output over the years? To quote Michael Welch again "*Why are other companies not pursuing radiopharmaceuticals utilizing the group?" The first and the most obvious answer to that question is that companies are loathe pursuing approaches where the patent is assigned to a competitor.*"[14] This may be one of the reasons. Another reason mentioned in that paper and becoming more prominent over the last decade is the emerging excitement about positron emission tomography (PET) which has become a strong competitor for SPECT. The fact that still around 80% of all diagnostic procedures in nuclear medicine is certainly true, despite this competition, but they are essentially all with compounds that are more than twenty years old.[15]

Despite patenting most of the research outputs coming from the research fees provided by the original patent assignee, there was little interest in bringing a ^{99m}Tc-based radiopharmaceutical to the market. To have research fees from a company as a university institution is often double-edged since the freedom of research at university does not necessarily parallel the interests of companies. However, as the Isolink® kit development showed, requests and constraints from companies may be incentives to find new approaches also of interest for fundamental research. In this spirit, it is important that companies name a specific target or targeting molecule to be labelled with e.g. the carbonyl technology in the present context. This completes the sequence application – research – application, which is ideal for cooperations between partners from the private and the academic sector. Mallinckrodt Med. B.V. lead us complete freedom in our research directions with ^{99m}Tc, beneficial for producing more fundamental insights, but malignant for the development of new radiopharmaceuticals. We learned from l**esson 9** that the assignment of a not too specific but strategic objective for and by the partner is essential. The company should give guidelines, e.g. from a marketing evaluation, but should not specify too narrowly about how to get there. Such a market-oriented setting does not affect research freedom and may lead to a product indeed. These guidelines were clearly missing during the first decade of the carbonyl technology.

The excitement about the *fac*-[^{99m}Tc(CO)$_3$]$^+$ core and the realm of related opportunities inspired many cooperations and investigations. The high robustness of imidazole coordination for instance inspired a direct labelling of recombinant single chain antibodies scFv, which often carry his-tags. These his-tags can conveniently and directly be labelled without the introduction of a bifunctional chelator due to the high affinity of the *fac*-[^{99m}Tc(CO)$_3$]$^+$ core for histidine (Scheme 2).[16]



Scheme 3. A complex with two "agostic" Tc-H interactions (a), an LAT1 targeting complex mimicking an amino acid (b) and a myocardial imaging agent with equal properties than Cardiolite® (c).

Many publications appeared and are still appearing which applied this strategy but to our knowledge, none led to a product.[16a, 16d, 17] In the context of scFv's, the name "Isolink®" proved correct since the targeting molecule and the label could be combined by simple mixing. Depending on the length of the linker, different

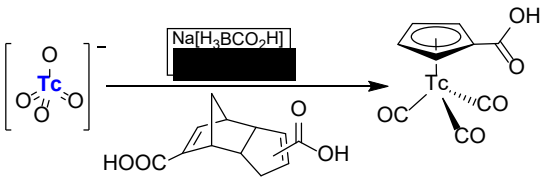
histidines may be labelled, resulting in principle in different radiopharmaceutical. However, the change is small in comparison to the size of the protein and they are not distinguishable.

A very fruitful and long-standing cooperation was established with the group of Isabel Santos at the University of Lisbon, Portugal. This cooperation concerned fundamental chemistry and application in radiopharmaceuticals. The robustness of the *fac*-$[^{99m}Tc(CO)_3]^+$ core led to very uncommon complexes, e.g. a complex with a kind of an agnostic ^{99}Tc-H interaction that proved to be very stable even for ^{99m}Tc under biological conditions (Scheme 3a). This complex was obtained in quantitative yields with the ligand at micromolar concentrations.[18] Our attempts to target the L-type amino acid transporter LAT1 is a similar category. This transporter is highly overexpressed on many cancer cells and may offer an alternative to the glucose transporter GLUT-1, so decisive for the success of the PET radiopharmaceutical [^{18}F]FDG.[19] The very small and highly potent tripod ligand 1,2-diaminopropionic acid was attached to an amino acid functionality and labelled with the *fac*-$[^{99m}Tc(CO)_3]^+$ core at micromolar concentrations. The resulting complex was actively transported by LAT1 and internalized, representing thus the first small molecule labelled with ^{99m}Tc that was recognized and transported by an antiport trans-membrane transporter (Scheme 3b).[20] The concept was not pursued since the company lost interest.

The Lisbon group presented a myocardial imaging agent with *in vivo* properties equal or even better than the gold standard Cardiolite® (Scheme 3c). The compounds and the concept were patented but not pursued by the company.[21]

To widen the scope of the *fac*-$[^{99m}Tc(CO)_3]^+$ core and the carbonyl technology, an extension to smaller tripod-like ligands was sought in the form of cyclopentadienyl (Cp) complexes, the very original incentive which lead ultimately to the carbonyl technology (vide supra). Inspired by the work of Gérard Jaouen[22] and coworkers on ferrocifens, the concepts of first and second generation radiopharmaceuticals[23] is to be extended to an integrated approach, comparable to the ferrocifen strategy. Although piano-stool type ^{99m}Tc complexes had already been prepared by Wenzel, Katzenellenbogen, and coworkers, their synthetic approaches were not convenient for routine production of Cp-conjugated radiopharmaceuticals.[24] Attracted by this challenge, we developed a fully aqueous route with Cp compounds of ^{99m}Tc bearing a carbonyl group directly attached to the Cp ring. With these derivatives, it was possible to label e.g. a serotonergic receptor ligand with the *fac*-$[^{99m}Tc(CO)_3]^+$ core in a one pot reaction directly from $[^{99m}TcO_4]^-$.[25] From this, we learned in **lesson 10** that essentially any water stable ^{99m}Tc complex can be prepared directly from $[^{99m}TcO_4]^-$, an implication which became decisive in our latest research (vide infra).

This approach was though not very flexible in terms of conjugated targeting molecules since the cyclopentadiene ligand tends to undergo Diels-Alder di- and polymerization. The same is true for cyclopentadiene-carboxylic acid, which converts rapidly in its dimer, so-called Thiele's acid ($[C_5H_5\text{-}COOH)]_2$). At a first glance, we considered this compound to be a "dead end" since retro-Diels-Alder reactions occur typically above about 160°C. We still subjected Thiele's acid to a reaction with $[^{99m}TcO_4]^-$ and found to our surprise that the piano-stool $[(\eta^5\text{-}C_5H_4\text{-}COOH)^{99m}Tc(CO)_3]$ formed in quantitative yields already at 100°C. Since retro Diels-Alder does not happen at this temperature at all, we concluded that we had a case of a metal-mediated retro Diels-Alder reaction.[26] **Lesson 11:** try, sometimes it works even if you do not believe in it. This motto accompanied us from the beginning when preparing the $[^{99m}Tc(OH_2)_3(CO)_3]^+$ throughout our research (Scheme 4).

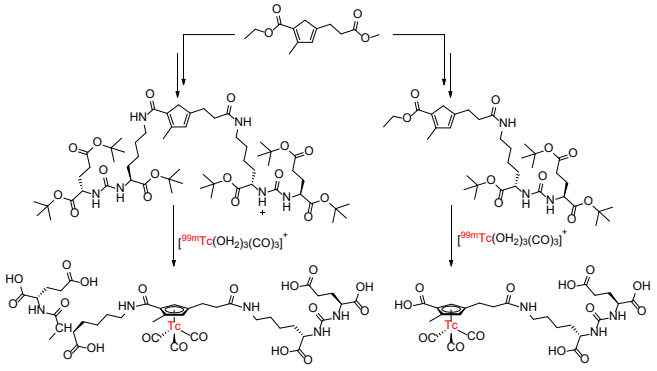


Scheme 4. The "one pot" preparation of a piano-stool complex with ^{99m}Tc in water and from $[^{99m}TcO_4]^-$. The acid groups may be functionalized.

Since Thiele's acid is a very stable molecule, many targeting functions can conveniently be conjugated to it. We did so for instance with carbonic anhydrase (CA) targeting sulphonamide derivatives.

Some CA subtypes are highly overexpressed on cancer cells. They therefore represent attractive targets for molecular imaging.[27] Some of the rhenium homologues bound with low nanomolar affinities to CA receptors. The most amazing fact was the higher specificity for interesting receptor subtypes, which was much more distinct than what was found for organic molecules. This finding confirms the matched-space concept for bioorganometallic drugs as introduced by Eric Meggers and coworkers.[28]

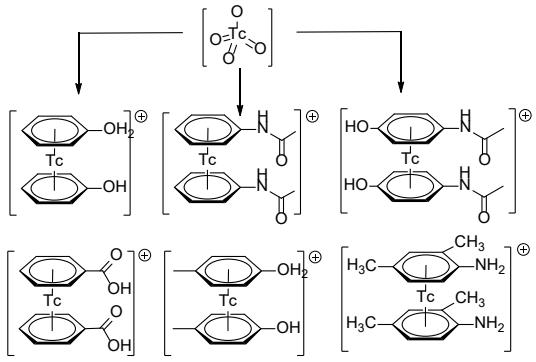
At that time, interest in ^{99m}Tc chemistry for radiopharmaceuticals was essentially extinct by the companies. Still, we pursued the cyclopentadienyl concept since it may lead us in the only field in which ^{99m}Tc might have a chance in the future; the integrated or the biomimetic concept towards theranostics. Whereas the biomimetic concept is standard in the medicinal inorganic chemistry community, it is not in molecular imaging or radiopharmaceuticals. Along a purely organic approach, we could derivatize the Cp-ring in a way, which allowed the conjugation of multiple bioactive units. The piano-stool complex thus mutated from a pendent part of a molecular imaging agent to a structure integrated in two (or more) identical or different moieties. Biological studies with PSMA for instance showed that two receptor-binding motives were better than the sum of two individual ones (Scheme 5).[29]



Scheme 5. Multi-functionalized cyclopentadienyl rings and labelling with ^{99m}Tc.[29b]

According to current concepts in bioorganometallic chemistry, the cyclopentadienyl ring of a piano-stool complex shall mimic a phenyl ring in a lead structure, the relationship ferrocifen-tamoxifen being one of the most prominent examples (vide supra). However, a cyclopentadienyl is not a phenyl and a proper mimic would not replace the later motif by the former. The theranostics idea behind is to apply homologues for which the ^{99m}Tc compound is the imaging agent and the rhenium complex the therapeutically active congener. Producing true mimics of phenyls means preparing arene complexes. Arene complexes are typically prepared under Fischer-Hafner conditions, which are obviously a "no go" for radiopharmaceuticals.[30]

Learning from → lesson 11, we tried and were finally successful in preparing a full series of ^{99m}Tc complexes of the form $[^{99m}Tc(\eta^6\text{-arene})_2]^+$. The syntheses directly from the generator eluate and in saline are applicable even to highly functionalized arenes.[31] Although conditions have to be adapted from arene to arene, complexes with essentially all of them work, albeit, if not optimized, in variable yields (Scheme 6).

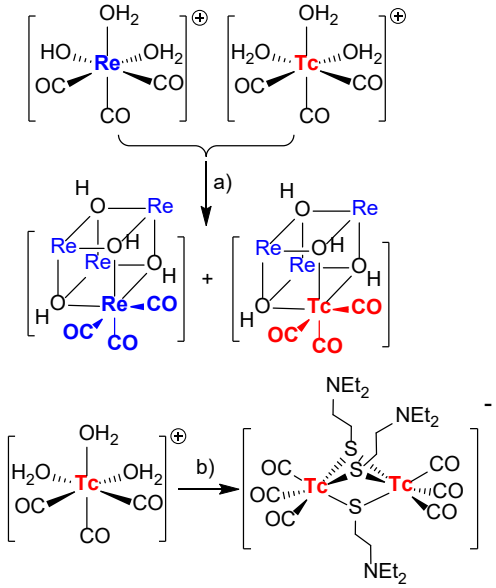


Scheme 6. Direct preparation of bis-arene complexes of ^{99m}Tc from water and starting from $[^{99m}TcO_4]^-$.[31]

With this preparation, we were in a peculiar situation, rarely if ever encountered in radiopharmaceutical chemistry before. We showed for many examples the nature of the ^{99m}Tc bis-arene complexes by comparing HPLC retention times with the fully characterized rhenium homologues. However, these rhenium homologues can hardly be prepared for highly functionalized arenes such as found in typical pharmaceuticals. Thus, very new synthetic routes to this very old class of organometallic compounds have to be developed; application inspires basics. **Lesson 12**, try! (Scheme 6).

When doing chemistry with ^{99m}Tc, concentrations are highly diluted, typically in the low to high nanomolar range. This is generally considered as a disadvantage since any classical analytical techniques are not applicable. The only way to characterize a ^{99m}Tc compound is by HPLC comparison to its rhenium or ^{99}Tc homologue, as practiced in most research groups. However, this comparison is sometimes not bijective, especially when comparing rhenium with ^{99m}Tc. It has been a paradigm for a long time that for these concentration reasons, di- or multinuclear complexes of ^{99m}Tc complexes do not exist. Since the solutions are highly dilute, the formation of even binuclear complexes can be excluded for kinetic reasons. Despite these "disadvantages", the high dilution factor also comes along with advantages we are not so much aware. The formation of side products in thermodynamic sinks such as to $^{99m}TcO_2$ is strongly disfavoured or even suppressed, also for kinetic reasons. This is immediately obvious from the fact that none of the syntheses aforementioned is applicable to ^{99}Tc under the same conditions, apart from the concentration. Without exception, they all end up in $^{99}TcO_2$ (or ReO_2) with the formation of no or minute amounts of product. The dilution and only the dilution make these compounds accessible at all. We learn thus in **lesson 13** that even highly unlikely complexes or labelled compounds, such as the ones mentioned before, may be accessible for kinetic reasons. This again nourishes the notion of "trying".

Considering the "high dilution" factor as relevant for the formation of uncommon complexes, we showed recently the formation of mixed Re/^{99m}Tc clusters.[32] Clusters are essentially not taken into account in medicinal inorganic chemistry. Still, their self-assembly in the presence of non-radioactive carriers could open a new field. Within the same context, we showed for the first time that dinuclear $^{99m}Tc_2$ complexes do exist. If mechanisms and rates



Scheme 7. Preparation of mixed ^{99m}Tc/Re cluster by self-assembly (a) and dinuclear $^{99m}Tc_2$ complex from highly diluted solutions.[33]

match, multinuclear ^{99m}Tc complexes might exist and also account for unidentified side-products in common syntheses (Scheme 7).[33]

What do all these experiences with companies and the presented chemistry imply? First, scrutinize if patenting is worthwhile at all. Is there a slight chance that the patented science is likely to turn into a product? It is attractive to state, "we have a patent". To be granted and to maintain a patent is often a lot of tedious and unproductive work. If you have one, it does not mean you have something useful. Aspects to be considered and experience of this author with patenting (which are purely subjective) as well as the hurdles to turn an invention into a product in the life science field have been given in the first sections of this report.

Risk the unlikely (but only if certain prerequisites are given)! We learnt for instance from basic chemistry research with the known $[Re(\eta^6\text{-}C_6H_6)_2]^+$-type complexes and their ^{99}Tc homologues that

they displayed an extreme stability.[34] This is an essential property for a radiopharmaceutical, but the question is, how to prepare it … and a way was found. This strategy proved correct for most of our novel complexes and underlying concepts.

Even if no molecular imaging agents or radiopharmaceuticals result from this strategy, going for novel building blocks and cores still allows doing interesting research, which may outreach in not immediately obvious fields such as CO releasers or into vitamin B12 chemistry in our case. Equally important is to watch related disciplines such as medicinal inorganic chemistry. The concepts applied there may guide into new options for imaging, which are complementing their efforts.

The finding of new building blocks is challenging but may be the only way to give ^{99m}Tc eventually its traditional importance back for nuclear medicine. These are the lessons from what we learnt over the years in general and with the carbonyl technology in particular. Numerous groups published excellent studies with this technology, very few compounds even made it to patients and only one has made it through the clinical phases. As in pharmaceutical research from discovery to development to the bedside, this is though not the exception but the rule. The author hopes that Rotop Pharmaka will bring MIP-1404 to the European Market.

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Disclaimer

The author disclaims that the content of this report is his personnel perception and experience with the “Carbonyl Story” and may not coincide with the views of companies.

Keywords: Carbonyl Technology • Technetium • Molecular Imaging • Patenting, • Bioorganometallics

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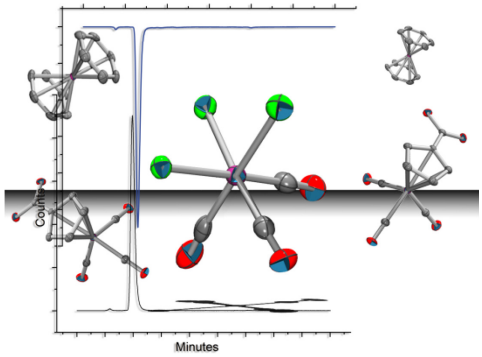

The way to bring a ^{99m}Tc imaging agent into and through clinical trials is a long one. Although the “Carbonyl Technology” is known since almost two decades, only one compound made this track. The different reasons for this is discussed in the paper together with scientific developments inspired by but beyond the carbonyl technology.