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CURRENT LANDSCAPE IN CLINICAL PRETARGETED RADIOIMMUNOIMAGING AND THERAPY

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ABSTRACT

The principle of pretargeted radioimmunoimaging and therapy has been investigated over the past 30 years in preclinical and clinical settings with the aim of reducing the radiation burden of healthy tissue for antibody based nuclear medicine techniques. In the past few decades, four pretargeting methodologies have been proposed, and two of them, the bispecific antibody-hapten and the streptavidin-biotin platforms, have been evaluated in humans in phase 1 and 2 studies.

With this review article, we aim to survey clinical pretargeting studies in order to understand the challenges that these platforms have faced in human studies and to provide an overview of how the clinical approval of the pretargeting system has proceeded in the past several decades. Additionally, we will discuss the successes of the pretargeting human studies and compare and highlight the pretargeting approaches and conditions that will advance clinical translation of the pretargeting platform in the future.

INTRODUCTION

Pretargeted nuclear imaging and therapy is an alternative approach for conventional antibody based nuclear medicine techniques. (1) Pretargeting combines the specificity of a tumor targeting antibody with the pharmacokinetic profile of a radiolabeled small molecule (radioligand) to reduce the overall radiation dose associated with the use of directly radiolabeled antibody nuclear medicine agents. In 1985, Reardan et al. first introduced the concept of pretargeting in which a pre-administered tumor targeting antibody interacts *in vivo* with high specificity with a small molecule radioligand, commonly referred to as “bioorthogonal” reactivity. (2) They reported a preclinical study of successful pretargeting using a bispecific antibody (bsAb) targeting a tumor antigen and an ethylenediaminetetraacetic acid chelate complex radioligand. Two years later, in 1987, Hnatowich et al. reported the use of another pretargeting approach in a preclinical model where the pretargeting interaction between the tumor bound antibody and the radioligand

occurred via high affinity avidin-biotin association. (3) In total, four pretargeting mechanisms have been proposed and evaluated *in vivo* in preclinical studies (Fig. 1), and these have been reviewed by other groups previously. (1,4)

To date the streptavidin-biotin and the bsAb-hapten pretargeting platforms are the only systems that have been evaluated in humans. Since the first reported human studies of the streptavidin-biotin and bsAb-hapten approaches in 1990 and 1993 respectively, (5,6) over 30 reports describing original pretargeting studies in humans have been published. (Fig. 2) Both approaches have proven capable of lowering the radiation burden to healthy tissue compared to conventional antibody based nuclear medicine. In this review, we discuss the challenges and successes of both of the approaches in the clinic and what possible directions upcoming pretargeting strategies need to take to result in a first clinical application of the approach.

STREPTAVIDIN-BIOTIN PLATFROM IN THE CLINIC

The strong non-covalent interaction between streptavidin and biotin ($K \sim 10^{14}$ M^{-1}) has made the molecule pair desirable for many applications in biomedicine, and it has been applied to pretargeting as well. The streptavidin-biotin approach has been evaluated in humans for pretargeted scintigraphy (5,7) and radioimmunotherapy. (8-13) (Table 1) A majority of the pretargeted streptavidin-biotin human studies have been done using full length tumor targeting antibodies conjugated with either biotin or streptavidin along with a clearing agent (CA) that is given prior to the biotin radioligand administration.

At the turn of the millennium, multiple human studies were performed evaluating pretargeted ^{90}Y-radioimmunotherapy in patients with non-Hodgkin's lymphoma, glioma and gastrointestinal carcinoma. In 1999, Paganelli et al. produced the first set of promising results showing reduction of tumor burden in 25% of their high-grade glioma patients after one cycle of pretargeted ^{90}Y-

biotin radioligand. (8) Later, Paganelli et al. also reported an overall 25% response rate in recurrent grade II glioma and anaplastic astrocytoma patient cohorts. (14) Around the same time, Grana et al. published a pretargeted ^{90}Y-radioimmunotherapy study in high-grade glioma patients resulting in a median survival of 33.5 months compared to the 8 months of the control cohort. (15) These promising results established the feasibility of the approach in human therapy and led to greater interest in the pretargeting concept, accelerating research in the field.

Almost all the clinical trials that have been performed using a three-step method have included the use of a streptavidin and/or avidin or a biotin-galactose based CA. (10,12,16) The use of biotin-galactose derivatives as CAs prior to radioligand injection has been shown to dramatically decrease the presence of accessible antibody conjugate in the blood pool and to efficiently decrease the required lag time between the antibody and radioligand administrations. (10,12) Interestingly, despite the use of the three-step approach and the evidence of its effect in reducing the antibody concentration in the blood pool, hematological toxicity has appeared as a reoccurring difficulty in the streptavidin-biotin based ^{90}Y-pretargeted radioimmunotherapy studies. (8,9,15) To address the issue, Breitz et al. reported the effects of different pretargeting parameters by adjusting the interval time and the dosing of the streptavidin-antibody conjugate, clearing agent, and ^{90}Y-biotin. (16) This optimization produced a pretargeting protocol which resulted in no hematological toxicities in their patient population with various adenocarcinomas. However, the study did not report whether or not the optimized protocol resulted in a tumor uptake sufficient enough to show a clinical response.

In addition to the challenges with hematological toxicity, the streptavidin-biotin platform has been marked by high incidence of immune response to the streptavidin- and avidin-based pretargeting agents. Development of anti-streptavidin or anti-avidin antibodies in patients has been observed in all of the clinical trials that reported an investigation of their immunogenicity studies. (5,7-10,12-

14,16) Despite several clinical evaluations of the platform's safety and efficacy, the immunogenicity of the pretargeting agents has not been addressed. Preclinical investigation of the platform is still ongoing, but its clinical evaluation has ceased with the last reported clinical trial in 2005.

BISPECIFIC ANTIBODY-HAPTEN PLATFORM IN THE CLINIC

In addition to the streptavidin-biotin methodology, the bsAb-hapten platform has been widely studied in the clinical setting. (Table 2) Two different strategies for bsAb-hapten pretargeting approach have been studied clinically. Starting in 1993, with the first clinical trial of bsAb-hapten pretargeting approach, the majority of clinical trials have used fragmented bispecific antibodies (Fab-Fab') along with a radiolabeled mono- or bivalent chelate complex serving as radioligand. This contrasts with the utilization of a CA as with the streptavidin-biotin system. The use of fragmented antibodies leads to a more rapid blood pool clearance of the antibody constructs due to the smaller size, and elimination of the Fc region the antibody construct negates the interaction with the neonatal Fc receptor further reducing the circulating half-life of the constructs. The overall effect of this approach is reduced intervals between administration of the targeting construct and radioligand, reduced potential for hematological toxicity, and presumably an improvement in tumor to tissue uptake ratios.

In 2013, Schoffelen et al. reported the use of a bispecific trivalent antibody construct (Tri-Fab) in tandem with a histamine-succinyl-glycine (HSG) peptide based hapten radioligand. Since then, all the reported bsAb-hapten clinical trials have used the Tri-Fab-HSG-hapten strategy. Comparing the two approaches, the Tri-Fab-HSG-hapten strategy has shown more promising results, providing excellent specificity and sensitivity for pretargeted PET imaging for patients with varying cancer profiles. Additionally, one of the major advantages of using peptide based haptens compared to the chelate complex haptens, is the ability to design a library of peptide haptens

accompanied with different radionuclides with lowered risk of changing the haptens' binding to the antibody.

To date, the evaluation of the Tri-Fab-HSG-hapten approach in humans has included the use of only one antibody construct, a carcinoembryonic antigen (CEA) targeting humanized Tri-Fab bsAb called TF2. (17,18; NCT00860860) This trivalent bsAb TF2 construct has been tested along with an HSG hapten called IMP288 for pretargeted PET imaging (^{68}Ga-IMP288) (19-21; NCT01730638, NCT01730612) and radioimmunotherapy (^{111}In/^{177}Lu-IMP288) (17,18,22; NCT00860860, NCT01221675) in patients with colorectal cancer, medullary thyroid carcinoma, EGFR2-negative breast cancer and metastatic lung cancer. ^{90}Y- and ^{111}In-radiolabled derivatives of IMP288 are being tested in a clinical setting as well. (20; NCT02587247, NCT02300922) The most recent work with the TF2-^{68}Ga-IMP288 pretargeting pair has resulted in higher sensitivity and specificity in detecting tumor lesions in metastatic colorectal cancer patients compared to FDG-PET. (20; NCT02587247) The CEA targeted pretargeting pair was also shown to be highly capable of detecting lesions in patients with HER2-negative metastatic breast cancer. (21; NCT01730612) In that setting, the pretargeted immuno-PET showed higher overall sensitivity (94.7%) relative to FDG-PET (89.6%). (Fig. 3) The number of true positive lesions detected in lymph nodes, bone and liver was higher using immuno-PET than FDG-PET. Those exciting results have clearly exhibited the potential for pretargeted PET imaging in cancer.

As mentioned earlier, immunogenic response to the pretargeting agents has been a limitation of the streptavidin-biotin system. Immunogenicity of the bsAb constructs has been observed in the bsAb-hapten platform as well. Barbet et al. reported that a high percentage of their patients (61%) developed human antimouse antibodies (HAMA) when a fully murine anti-CEA × anti-DTPA bsAb was administrated as part of the pretargeting protocol. (23) More recent trials have used mouse/human Fab-Fab' bsAbs which has decreased the prevalence of HAMA development in

patients. (24; NCT00467506) Yet, development of human antihuman antibodies (HAHA) against mouse/human pretargeting bsAb agents has been shown to occur as well. (24-26; NCT00467506) It should be noted that bispecific antibody fragments tend to suffer from aggregation issues which can induce an immunogenic response. (27) However, Barbet et al. observed formation of high molecular weight aggregates and noticed a decrease in the HAMA induction after improving the production and purification process of the antibody fragment, indicating this problem can be overcome by appropriate formulation. (23) Furthermore, premedication with an antihistamine and corticosteroid has been shown to reduce the prevalence of immunogenic response in patients. Using this approach, Touchefeu et al. reported that no patient (n_{total} = 11) developed HAHA in their TF2-^{68}Ga-IMP288 pretargeted PET study. (20; NCT02587247) Rousseau et al. shared similar results, observing immunogenic response in only 16% of patients (n_{total} = 23) with the antihistamine and corticosteroid premedication. (21; NCT01730612)

Many bsAb-hapten clinical trials have investigated the use of different pretargeting schedules and protocols to define the conditions that result in the highest tumor-to-background ratios and lowest radiation-induced toxicity. (17,19,22,25,28,29; NCT00860860, NCT01730638, NCT01221675) This is done by optimizing the amount of injected doses of each of the pretargeting components, the stoichiometric relation between these agents, and the interval time separating the administration of the doses. The interval time applied in the clinical pretargeting studies has varied between 1-7 days and increasing the interval time has resulted in lower toxicity and better image quality to a certain extent. Schoffelen et al. showed that patients who received the ^{177}Lu-IMP288 hapten radioligand 1-day post TF2 antibody injection experienced significantly higher red marrow doses compared to patients who received the radioligand 5 days post antibody injection. (17; NCT00860860) Bodet-Milin et al. reported that increasing the interval time from 24 hours to 30 hours decreased the mediastinum blood pool (MBP) values, while a 42 hour delay time resulted

in lower tumor maximal SUV (T-SUV_{max}) and T-SUV_{max} to MBP ratios compared to the 30 hour lag time. (19; NCT01730638)

From the point of view of adjusting both the interval time and the dosing, Kraeber-Bodéré et al. observed that a 5-day interval time resulted in a better tumor uptake of the hapten compared to 7-day interval time. However, the tumor uptake increased and the tumor localization was visible even with the 7-day interval time when the bsAb dose was increased from 10 mg/m^2 to 50 mg/m^2. (28) Certainly, one of the challenges for all of the pretargeting platforms is that each combination of target antigen, antibody construct, and radioligand requires its own pretargeting protocol, which will be a challenge when pretargeting is applied to a variety of different cancers for diagnostic and therapeutic purposes.

Surprisingly, direct comparison of pretargeted to the directly-labeled approach using the same targeting molecule within the same patient population has not been performed extensively. Kraeber-Bodéré et al. have compared the dosimetry of a CEA-targeting ^{131}I-labeled bsAb to the pretargeted ^{131}I-hapten. The ^{131}I-bsAb's dosimetry was first determined by scintigraphy over the several day interval time. This was followed by an injection of the ^{131}I-hapten and study of its dosimetry. (28) With two different pretargeting conditions (75 mg/m^2; 5 day interval or 100 mg/m^2; 7 day interval), the tumor-to-whole body ratios were significantly higher for the pretargeted hapten compared to the directly labeled antibody. Additionally, the calculated tumor radiation doses where higher with the pretargeted ^{131}I-hapten compared to the directly labeled ^{131}I-bsAb (3.9 Gy/GBq and 2.0 Gy/GBq respectively). The study showed that their pretargeting approach was superior to the directly labeled approach, with tumor to whole body ratio of 55:1 for pretargeting (75 mg/m^2; 5 day interval) and 16:1 for the conventional approach using just the ^{131}I-bsAb. Perhaps more importantly, the study was a good example of how to optimize a pretargeting platform to achieve success in patients.

Over the past 30 years the bsAb-hapten platform has been studied consistently and upcoming clinical trials using the TF2-IMP288 pretargeting strategy are planned (NCT02300922, NCT01730638). The recent work with the platform holds a lot of promise in solidifying the use of the pretargeting approach as an alternative to the use of directly radiolabeled antibodies.

DISCUSSION

Clinical investigations of pretargeted nuclear imaging and therapy have shown the utility of the pretargeting approach in overcoming the high overall radiation doses of conventional radioimmunoimaging and therapy. Both of the discussed pretargeting platforms are successful at lowering the overall radiation dose, but they both have hurdles to overcome if their full potential is to be realized. In the case of streptavidin-biotin approach, the main challenge has been the immunogenicity of the streptavidin and avidin pretargeting constructs. During its 15-year period of separate clinical studies, the high prevalence of immunogenic response to the pretargeting agents was not addressed. Also, the addition of a third molecule (e.g. clearing agent) to the pretargeting protocol makes it a more complicated approach, due to the need to optimize the CA dosing. These concerns compared to pretargeting platforms such as bsAb-hapten system, which have shown to work efficiently without a CA, put the streptavidin-biotin approach at a major disadvantage.

One major drawback of the bsAb-hapten approach is that it lacks modularity. The development of the HSG-haptens has been an improvement in this regard, but each bsAb agent targeting a different antigen of interest needs to be designed and engineered even if a clinical antibody already exists. The development of novel working bsAb agents is a time-consuming and costly process. Additionally, the bsAb constructs have faced a lot of challenges in their clinical translation and currently only two bispecific antibodies are approved for the clinical use. (27) Due to the increasing need for antibody based imaging and therapeutic nuclear agents, ideally the

pretargeting agents need to be developed and manufactured efficiently and affordably in order to access a wide variety of different tumor antigens.

In addition to the two platforms discussed in this review, other promising pretargeting methodologies are moving toward clinical evaluation as well. In the last decade the inverse electron demand Diels Alder (IEDDA) click chemistry pretargeting approach has been shown to work very well in preclinical models, delivering the radioligand to the target site with great specificity. As a result, the platform's first clinical trials, which will notably not utilize a CA, are reported to start soon (early 2021). (30) Compared to the bsAb-hapten approach, the click chemistry pretargeting components — a transcyclooctene conjugated antibody and a tetrazene based radioligand — are highly modular, but the stability of the IEDDA pretargeting agents may prove a challenge for clinical translation. (31,32) With the first clinical trials poised to begin in 2021, the magnitude of this challenge will be revealed soon.

One of the main criticisms of all pretargeting approaches is the requisite use of non-internalizing or slowly internalizing antibodies, which limits the number of antibodies that can be used. Although the use of slowly internalizing antibodies such as CA19.9-targeting 5B1 and rapidly internalizing epidermal growth factor receptor (EGFR)-targeting cetuximab have been possible in a preclinical setting (33-35), it has yet to be reported in clinical studies. However, clinical translation will soon be attempted with the IEDDA-based approach and the slowly internalizing 5B1 antibody, which will help to more concretely determine what is possible in patients. It should be also noted that the process of antigen-antibody internalization is not always absolute. In preclinical studies internalizing TF12 bsAb was shown to remain accessible for hapten binding due to the only partial internalization of the antibody construct. (36) If those types of antibodies are successful in a clinical setting, it would increase the number of antibodies and molecular targets that can become part of the pretargeting tool kit, expanding the effectiveness of the approach.

In addition to imaging, pretargeting has immense potential to enhance radioimmunotherapy. Conventional radioimmunotherapy has shown good results in clinical response in patients with non-solid tumors. However, solid tumors possess higher radio resistance and, relative to non-solid tumors, five- to ten-fold radiation doses are required to achieve a response. (37) Since pretargeting produces faster delivery of the radiation source to the target site, larger doses could theoretically be administered with pretargeted radioimmunotherapy without inducing hematological toxicities. It is exciting that a large portion of the clinical studies of pretargeting platforms have been for pretargeted radioimmunotherapy. However, phase 2 clinical trials have only shown modest efficacy for both platforms. In two different studies of bsAb-hapten pretargeting with a ^{131}I-radiolabeled bivalent hapten radioligand in patients with CEA positive cancer, Kraeber-Bodéré et al. reported no occurrence of complete or partial response. (25,38) In another bsAb-hapten radioimmunotherapy study in patients with metastatic medullary thyroid carcinoma, a disease control rate of 76.2% (n=32) was observed. (24) It should be noted that most of the patients enrolled in these pretargeted radioimmunotherapy studies were late stage cancer patients with high tumor burden and had already unsuccessfully undergone other forms of therapy. Also, in these studies only a single dose of therapeutic radioligand was administrated as a standalone therapy. As clinical use of this approach expands, it may be useful to explore how pretargeted radioimmunotherapy would perform when joined with other therapies and/or when administered as multiple doses.

On average, more than ten new cancer therapeutic antibodies enter late-stage clinical trials every year. (39) As the role of antibodies in cancer therapeutics has increased, the potential for using antibody-based imaging agents in profiling patients' tumor antigen landscape to predict therapeutic response is consequential and significant. For the past 30 years, pretargeting has been proposed as an alternative approach to conventional antibody-based nuclear imaging and

therapy. The approval rate of directly radiolabeled antibodies for clinical use has been low with only two FDA approved radioimmunoconjugates, ^{131}I-tositumomab and ^{90}Y-ibritumomab, being approved in early 2000s for non-Hodgkin's lymphoma. (37) According to a survey done by Schaefer et al. in the United States, one of the bigger concerns for oncologists and hematologists in the use of ^{131}I-tositumomab is the possible bone marrow damage that could preclude patients from further therapy. (40) As our understanding of how to effectively implement pretargeted radioimmunotherapy expands, the preclinical data strongly suggests these types of toxicities can be avoided, alleviating some of the concerns of physicians that want to utilize these strategies in the clinic.

Pretargeting is an approach that has shown significant promise in solving the challenge of relatively high radiation burden of the non-tumorous tissue that is associated in the use of radioimmunoconjugates such as ^{131}I-tositumomab and ^{90}Y-ibritumomab. Yet, the clinical data on the use of pretargeting has not been straightforward. The challenges with toxicity, immunogenicity and modularity have not been fully addressed, but progress is gaining momentum and the outlook for pretargeted imaging and therapy remains promising.

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FIGURES

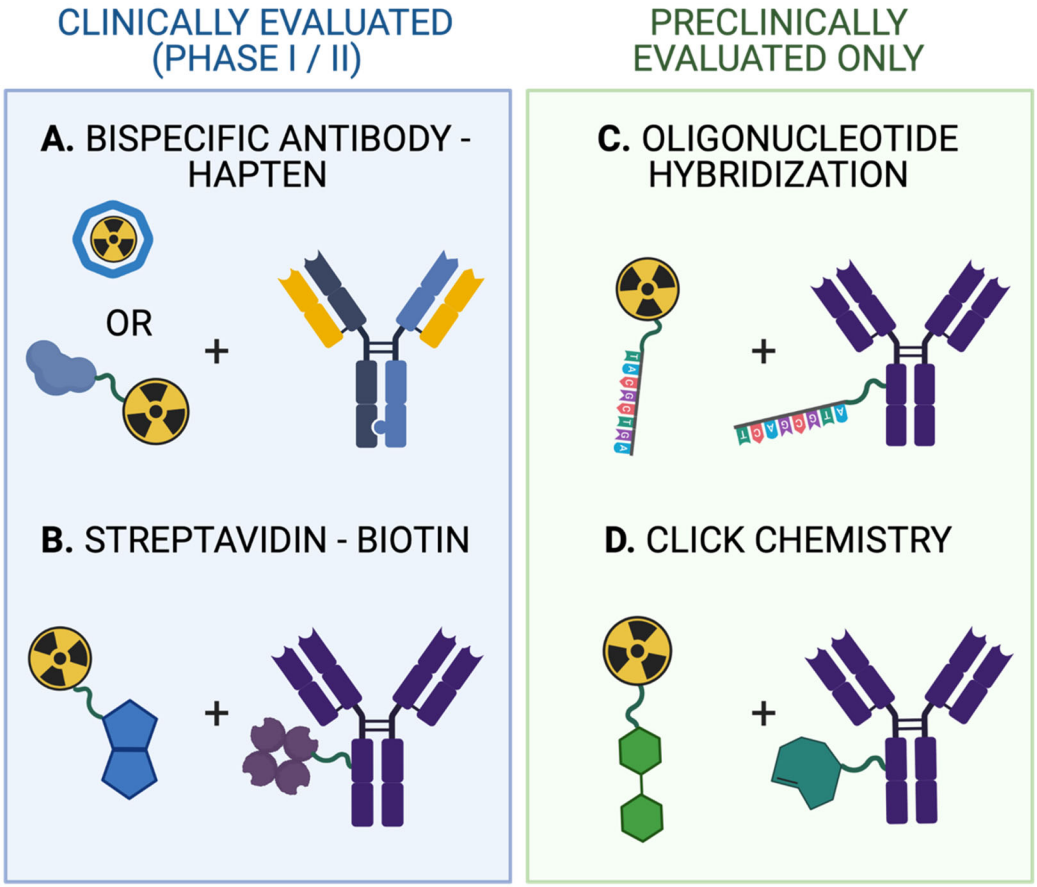

FIGURE 1. The pretargeting agents of the four main platforms that have been evaluated in clinical (A, B) or only in preclinical setting (C,D).

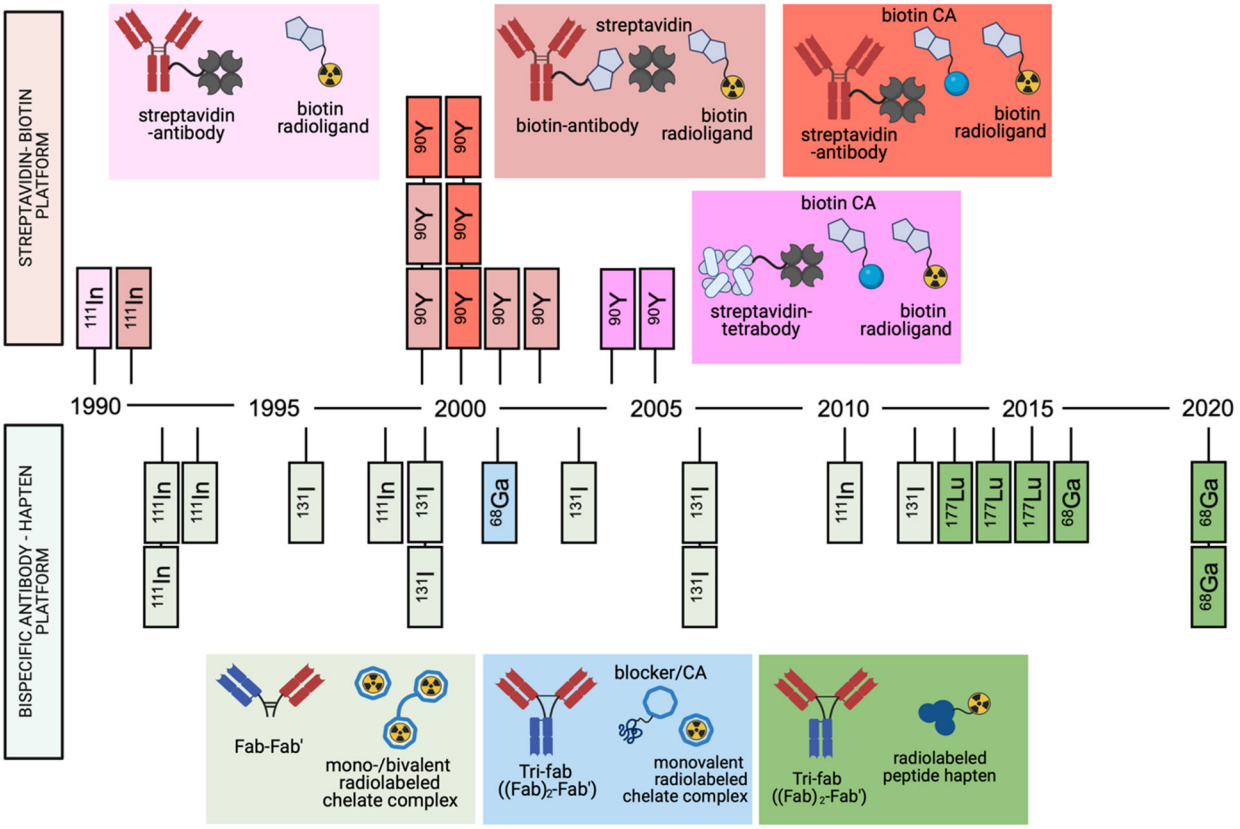

FIGURE 2. Timeline of the clinical studies of the bispecific antibody and the streptavidin – biotin pretargeting approaches. Each rectangle refers to a published report, with the radionuclide note referring to the primary radionuclide used in the study. The pretargeting agents used in each report are color coded.

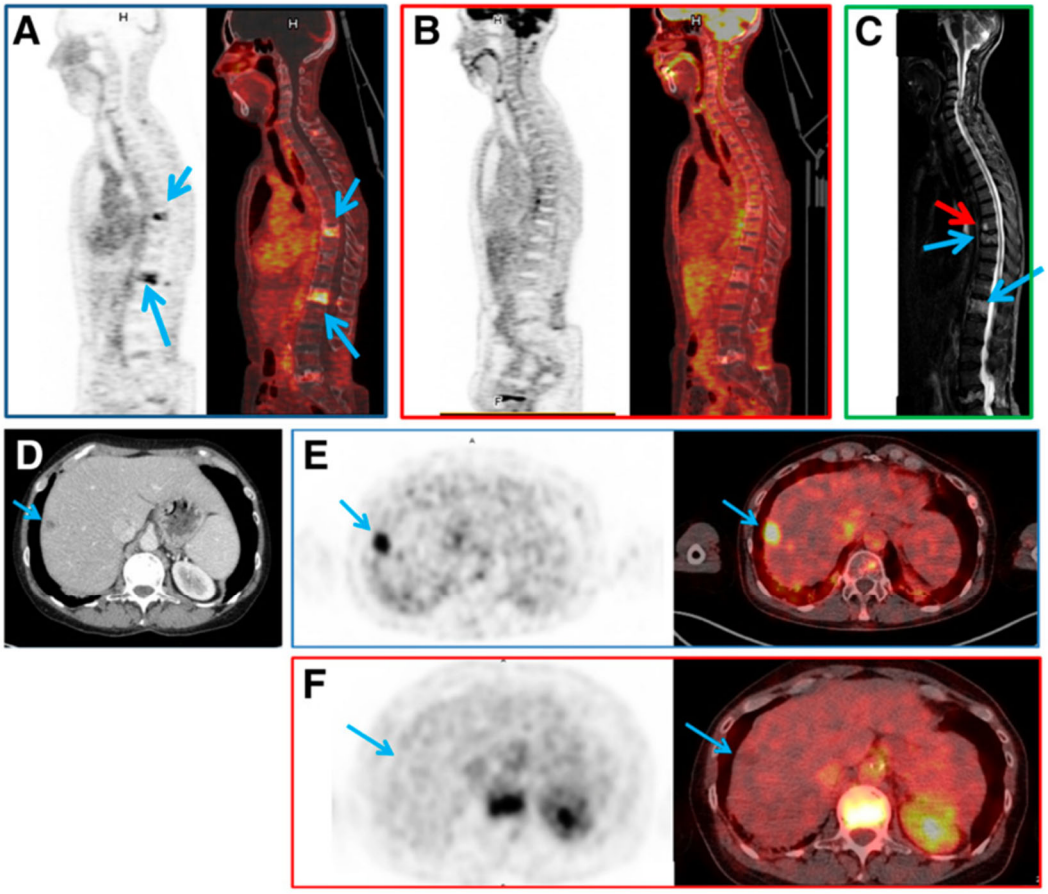

FIGURE 3. Rousseau et al. *J Nucl Med* 2020; 61:1205-1211 (21) (A–C) In patient 1, pretargeted immuno-PET with TF2 and ^{68}Ga-IMP288 peptide images show 2 vertebral metastases (L1 and T9, arrows) (A), ^{18}F-FDG PET discloses no vertebral abnormalities (B), and vertebral MRI confirms both lesions (blue arrows) and discloses another (red arrow) at T8 (C). (D–F) In patient 2, CT shows suspected liver lesion (D) and pretargeted immuno-PET with TF2 and ^{68}Ga-IMP288 peptide reveals high uptake by liver lesion (arrow) (E), which was not seen by ^{18}F-FDG PET (F).

TABLES

TABLE 1. Excerpts of human studies of pretargeted nuclear medicine using streptavidin-biotin system (CA; clearing agent, CR; complete response, SA; streptavidin, OS; overall survival)

Antibody radioligand pair & pretargeting timeline	**Radioligand dose**	**Target antigen & study population**	**Main Findings**	**Reference**
Hour 0: Biotinylated anti-tenascin mAb BC4 *Hour 36:* (strept)avidin CA *Hour 54-60:* ^{90}Y-DOTA-biotin	2.22-2.96 GBq/m^2	Tenascin & High grade glioma patients	Reduction in tumor in 25 % patients, all patients developed immune response	(8)
Hour 0: SA-conjugated C2B8 mAb *Hour 34:* biotin CA *Hour 52:* ^{111}In/^{90}Y-DOTA biotin	3-5 mCi (^{111}In) 30-50 mCi/m^2 (^{90}Y)	CD20 & Non-Hodgkin's lymphoma patients	Good tumor-to-whole body ratios (38:1), mild hematological toxicity, 2/10 patients with CR	(12)
Hour 0: SA-conjugated NR-LU-10 mAb *Hour 24-72 h:* Biotin-galactose-HSA CA *Hour 28-96 h:* ^{111}In/^{90}Y-DOTA biotin	185 MBq (^{111}In) 370 MBq/m^2 (^{90}Y)	Ep-CAM & Adenocarcinoma patients (majority colorectal and lung)	Good tumor-to-marrow absorbed dose ratio (63:1), all tested patients developed immune response	(16)
Hour 0: Biotinylated anti-tenascin mAb BC4 *Hour 24:* avidin CA *Hour 42:* ^{90}Y-DOTA-biotin (procedure repeated again 8-10 weeks apart)	0.555 – 1.110 GBq	Tenascin & Recurrent high-grade glioma, anaplastic astrocytoma patients	25 % overall response to PRIT, no hematological toxicity observed	(14)
Hour 0: Biotinylated anti-tenascin mAb BC4 *Hour 24-36:* avidin CA *Hour 40-54:* ^{90}Y-DOTA-biotin	2.2 GBq/m^2	Tenascin & High grade glioma patients	Significantly higher OS in treated cohort compared to control	(15)
Hour 0: SA-conjugated CC49-(scFv)$_4$ Hour 48/72: biotin CA Hour 62/96: ^{111}In/^{90}Y-DOTA biotin	185 MBq (^{111}In) 370 MBq/m^2 (^{90}Y)	TAG-72 & Metastatic colorectal cancer	Tumor-to-normal tissue dose ratio 54.5, immune response or toxicity not reported	(11)

TABLE 2. Excerpts of human studies of pretargeted nuclear medicine using bispecific antibody -hapten system (bsAb; bispecific antibody, CEA; carcinoembryonic antigen)

Antibody radioligand pair & pretargeting timeline	**Radioligand dose**	**Target antigen & study population**	**Main Findings**	**Reference**
Hour 0: anti-CEA × anti-DTPA indium bsAb *Hour 96-120:* ^{111}In-bivalent DTPA hapten	100-200 MBq	CEA & Medullary thyroid carcinoma	Immunogenic response in 61% of the patients. 80% true positive tumor visualization	(23)
Hour 0: hMN-14 × m734 bsAb *Hour 120/168*: ^{131}I-bivalent hapten	2.6-5.5 GBq	CEA & Varied patient population with CEA-positive tumors	Tumor dose of ^{131}I-bsAb and pretargeted ^{131}I-hapten 2.0 Gy/GBq and 3.9 Gy/GBq respectively. Tumor-to-whole body ratio higher with ^{131}I-hapten.	(28)
Hour 0: TF2 bsAb *Hour 24-30:* ^{68}Ga-IMP288 (premedicated with antihistamine and corticosteroid)	150 MBq	CEA & HER2-negative metastatic breast cancer	Immuno-PET showed higher total lesion sensitivity (94.7%) than FDG-PET (89.6%). Immunogenic response in 16% of the patients	(21; NCT01730612)
Hour 0: TF2 bsAb *Hour 30:* ^{68}Ga-IMP288 (premedicated with antihistamine and corticosteroid)	150 MBq	CEA & Metastatic colorectal cancer	Immuno-PET showed higher sensitivity (88%) and specificity (100%) than FDG-PET (76%; 67% respectively), no immunogenic response	(20; NCT02587247)
Hour 0: TF2 bsAb *Hour 24/120:* ^{111}In/^{177}Lu-IMP288	185 MBq (^{111}In) 2.5-7.4 GBq (^{177}Lu)	CEA & Advanced colorectal malignancy	10% patients experienced grade III-IV hematological toxicity, no therapeutic effect detected	(17,18; NCT00860860)