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# Immunotoxins Constructed with Ribosome-Inactivating Proteins and their Enhancers: A Lethal Cocktail with Tumor Specific Efficacy

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**Abstract:** The term ribosome-inactivating protein (RIP) is used to denominate proteins mostly of plant origin, which have *N*-glycosidase enzymatic activity leading to a complete destruction of the ribosomal function. The discovery of the RIPs was almost a century ago, but their usage has seen transition only in the last four decades. With the advent of antibody therapy, the RIPs have been a subject of extensive research especially in targeted tumor therapies, which is the primary focus of this review. In the present work we enumerate 250 RIPs, which have been identified so far. An attempt has been made to identify all the RIPs that have been used for the construction of immunotoxins, which are conjugates or fusion proteins of an antibody or ligand with a toxin. The data from 1960 onwards is reviewed in this paper and an extensive list of more than 450 immunotoxins is reported. The clinical reach of tumor-targeted toxins has been identified and detailed in the work as well. While there is a lot of potential that RIPs embrace for targeted tumor therapies, the success in preclinical and clinical evaluations has been limited mainly because of their inability to escape the endo/lysosomal degradation. Various strategies that can increase the efficacy and lower the required dose for targeted toxins have been compiled in this article. It is plausible that with the advancements in platform technologies or improved endosomal escape the usage of tumor targeted RIPs would see the daylight of clinical success.

**Keywords:** Targeted toxins, immunotoxins, ribosome-inactivating proteins, clinical application of toxins, tumor therapy, efficacy enhancer, endosomal escape enhancer.

## INTRODUCTION

### Ribosome-Inactivating Proteins (RIPs)

The term ribosome-inactivating protein (RIP) engenders a specific class of toxins, mostly of plant origin, which act predominantly on the ribosomal machinery *via* their *N*-glycosidase activity or polynucleotide adenosine glycosidase activity [1]. Although there is varying information about their mechanism of action, their enzymatic activity has drawn the most attention, especially relating to the anti-viral and anti-tumor effects [2]. In general, all RIPs are considered to be *N*-glycosidases, thus removing adenines from ribosomal RNA, and depurinating the conserved alpha-sarcin loop of the 28S ribosomal RNA (rRNA). This leads to the inhibition of protein synthesis, a vital process for cellular proliferation, and therefore leading to cell death [3].

The plant RIPs are further classified as type 1, 2 and in rare cases as type 3. Type 1 RIPs are characterized by the presence of only a toxic domain, whereas type 2 RIPs are the ones consisting of a toxin domain (A chain) together with a cell binding domain (B chain of lectin type). The B-chain facilitates its binding to the galactose residues on the cellular membrane, thus facilitating the cellular internalization. A further class of RIPs (type 3) has been proposed but the exact classification and occurrence are ambiguous. The literature description of type 3 RIP defines it as a protein which is evolutionarily related to a 60-kDa jasmonate-induced protein from barley, with RIP activity [4]. In total, there are nearly 250 RIPs that are scientifically described and the information pertinent to them was retrievable upon an extensive literature search. A summary of these RIPs with relevant literature reference and the botanical description is elaborated in Table **1**. The information provided includes the origin of the RIP, its type and the reported usage of this RIP as a targeted toxin.

While type I RIPs generally have lower toxicity, this is not predominantly because of their lack of enzymatic activity but contrastingly due to the missing B-chain making their cellular internalization cumbersome [5]. The missing cell binding domain is a blessing in disguise for molecular biologists, and has facilitated them to prepare fusion proteins or synthetic analogs of type 1 RIPs together with ligands that are able to facilitate their cellular internalization [6]. Moreover, in the recent decade, there has been a growing evidence that use of endosomal escape enhancers can lead to a significant augmentation of the efficacy of RIPs. This strategy has also paved a path for an improvement in the therapeutic utility of RIPs as targeted toxins or immunotoxins [5].

### Endocytosis, Cytosolic Delivery and Enzymatic Action of RIPs

The toxic potential of RIPs is determined by their ability to reach to the ribosomes, which are located within the cytosol. Thus, RIPs that are able to overcome cellular barriers end up exhibiting tremendous toxic potential. This overcoming of cellular barriers includes their internalization, which is generally facilitated by their B chain. Type 2 RIPs such as ricin from *Ricinus communis* L., abrin from *Abrus precatorius* L., or volkensin from *Adenia volkensii* Harms. [7] efficiently deliver their *N*-glycosidase domain (A chain) into the cytosol of intoxicated cells [8] which is facilitated by their B chains. The B chain serves as galactose/*N*-acetylgalactosamine binding domain (lectin) and is linked to the A chain *via* disulfide bonds.

After the binding with glycoproteins or glycolipids, which have numerous galactose residues on their surface, ricin is endocytosed *via* clathrin-dependent as well as clathrin-independent endocytosis and is thereafter delivered into the early endosomes. From there on

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**Table 1. RIPs isolated from different plants, their type and reported absolute molecular masses.**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Abelmoschus esculentus* (L.) Moench | Abelesculin | 1 | 30 | | [94] |
| *Abrus precatorius* L. | Abrin-a | 2 | 63 | Yes | [95] |
| *Abrus precatorius* L. | Abrin-b | 2 | 67 | | [95] |
| *Abrus precatorius* L. | Abrin-c | 2 | 63 | | [95] |
| *Abrus precatorius* L. | Abrin-d | 2 | 67 | | [95] |
| *Abrus precatorius* L. | Abrin-I | 2 | 64 | | [96] |
| *Abrus precatorius* L. | Abrin-II | 2 | 63 | | [96] |
| *Abrus precatorius* L. | Abrin-III | 2 | 63 | | [96] |
| *Abrus precatorius* L. | APA-I | 2 | 130 | | [96] |
| *Abrus precatorius* L. | APA-II | 2 | 128 | | [96] |
| *Abrus precatorius* L. | *Abrus* agglutinin | 2 | 67 | | [95] |
| *Abrus precatorius* L. | *Abrus* agglutinin | 2 | 134 | | [97] |
| *Abrus pulchellus* L. | Pulchellin | 2 | 61.5 - 63 | | [98, 99] |
| *Adenia digitata* Burtt-Davy | Modeccin | 2 | 57 | | [100] |
| *Adenia ellenbeckii* Harms. | *Adenia ellenbeckii* RIP | 1 | 30 | | [101] |
| *Adenia ellenbeckii* Harms. | *Adenia ellenbeckii* RIP | 2 | 60 | | [101] |
| *Adenia fruticosa* L. Burtt-Davy | *Adenia fruticosa* RIP | 1 | 30 | | [101] |
| *Adenia goetzii* Burtt-Davy | *Adenia goetzii* RIP | 1 | 30 | | [101] |
| *Adenia goetzii* Burtt-Davy | *Adenia goetzii* RIP | 2 | 60 | | [101] |
| *Adenia keramanthus* Harms. | *Adenia keramanthus* RIP | 2 | 60 - 65 | | [101] |
| *Adenia lanceolata* Engl. | *Adenia lanceolata* RIP | 2 | 60 | | [101] |
| *Adenia lanceolata* Engl. | Lanceolin | 2 | 61.2 | | [102] |
| *Adenia racemosa* W.J. de Wilde | *Adenia racemosa* RIP | 1 | 30 | | [101] |
| *Adenia stenodactyla* Harms. | *Adenia stenodactyla* RIP | 2 | 60 | | [101] |
| *Adenia stenodactyla* Harms. | Stenodactylin | 2 | 63.1 | | [102] |
| *Adenia venenata* Forssk. | *Adenia venenata* RIP | 1 | 30 | | [101] |
| *Adenia venenata* Forssk. | *Adenia venenata* RIP | 2 | 60 | | [101] |
| *Adenia volkensii* Harms. | Volkensin | 2 | 62 | | [103, 104] |
| *Agrostemma githago* L. | Agrostin-2 | 1 | 30.6 | | [105] |
| *Agrostemma githago* L. | Agrostin-5 | 1 | 29.5 | | [105] |
| *Agrostemma githago* L. | Agrostin-6 | 1 | 29.6 | | [105] |
| *Amaranthus caudatus* L. | Amaranthin (*Amaranthus caudatus* agglutinin, ACA) | 1 | 33 - 36 | | [106] |
| *Amaranthus tricolor* L. | *Amaranthus tricolor* antiviral protein-27 (AAP-27) | 1 | 27 | | [107] |
| *Amaranthus viridis* L. | Amaranthin | 1 | 30 | | [108] |
| *Aralia elata* (Miq.) Seem | Aralin (*Aralia elata* lectin) | 2 | 61.3 | | [109, 110] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Asparagus officinalis* L. | *Asparagus officinalis* RIP | 1 | 32.5 | | [105] |
| *Asparagus officinalis* L. | Asparin 1 | 1 | 30.5 | | [111] |
| *Asparagus officinalis* L. | Asparin 2 | 1 | 29.8 | | [111] |
| *Basella rubra* Roxb. | *Basella rubra* RIP 2a | 1 | 30.6 | | [112] |
| *Basella rubra* Roxb. | *Basella rubra* RIP 2b | 1 | 31.2 | | [112] |
| *Basella rubra*Roxb. | *Basella rubra* RIP 3 | 1 | 31.2 | | [112] |
| *Benincasa hispida* (Thunb.) Cogn. | Alpha-benincasin | Small RIP | 11 | | [113] |
| *Benincasa hispida* (Thunb.) Cogn. | Beta-benincasin | Small RIP | 10.6 | | [113] |
| *Benincasa hispida* (Thunb.) Cogn. | Hispin | 1 | 21 | | [114] |
| *Beta vulgaris* L. | Betavulgin | 1 | 28 | | [115] |
| *Beta vulgaris* L. | Beetin 27 | 1 | 27 | | [116, 117] |
| *Beta vulgaris* L. | Beetin 29 | 1 | 29 | | [116, 117] |
| *Bougainvillea spectabilis* Willd. | Bouganin (*Bougainvillea spectabilis* RIP) | 1 | 26.2 | Yes | [112, 118] |
| *Bougainvillea xbuttiana* Willd. | *Bougainvillea xbuttiana* antiviral protein | 1 | 35.5 | | [119] |
| *Bryonia dioica* Jacq. | Bryodin-L | 1 | 28.8 | | [111] |
| *Bryonia dioica* Jacq. | Bryodin-1 (BD-1) | 1 | 30 | Yes | [120] |
| *Bryonia dioica* Jacq. | Bryodin-2 (BD-2) | 1 | 27 | Yes | [121] |
| *Camellia sinensis* (L.) Kuntze | *Camellia sinensis* RIP (CS-RIP) | 2 | 63.6 | | [122] |
| *Celosia cristata* L. | *Celosia cristata* antiviral protein 25 (CCP-25) | 1 | 25 | | [123] |
| *Celosia cristata* L. | *Celosia cristata* antiviral protein 27 (CCP-27) | 1 | 27 | | [124] |
| *Charybdis maritima* L. | Charybdin | 1 | 29 | | [125] |
| *Chenopodium album* L. | *Chenopodium album* antiviral RIP (CAP30) | 1 | 30 | | [126, 127] |
| *Cinnamomum camphora* (L.) J. Presl. | Camphorin | 1 | 23 | | [128] |
| *Cinnamomum camphora* (L.) J. Presl. | Cinnamomin | 2 | 61 | | [128] |
| *Cinnamomum porrectum* L. | Porrectin | 2 | 64.5 | | [129] |
| *Citrullus colocynthis* Schrad. | Colocin 1 | 1 | 26.3 | Yes | [111] |
| *Citrullus colocynthis* Schrad. | Colocin 2 | 1 | 26.3 | | [111] |
| *Clerodendrum inerme* (L.) Gaertn | CIP-29 | 1 | 29 | | [130, 131] |
| *Clerodendrum inerme* (L.) Gaertn | CIP-34 | 1 | 34 | | [130, 131] |
| *Croton tiglium* L. | Crotin I | 1 | ND | | [132] |
| *Croton tiglium* L. | Crotin II | 1 | 30.2 | | [132] |
| *Cucumis figarei* Naud. | *Cucumis figarei* RIP (CF-RIP) | 1 | 31.8 | | [133] |
| *Cucumis melo* L. | Melonin | 1 | 23.5 | | [134, 135] |
| *Cucurbita foetidissima* Kunth. | Foetidissimin | 2 | 63 | | [136] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Cucurbita foetidissima* Kunth. | Foetidissimin II | 2 | 61 | | [137] |
| *Cucurbita maxima* L. | Cucurmoschin | Small RIP | 8 | | [138] |
| *Cucurbita moschata* Duchesne ex Poir. | Alpha-moschin | Small RIP | 12 | | [139] |
| *Cucurbita moschata* Duchesne ex Poir. | Beta-moschin | Small RIP | 12 | | [139] |
| *Cucurbita moschata* Duchesne ex Poir. | Moschatin | 1 | 29 | Yes | [140] |
| *Cucurbita moschata* Duchesne ex Poir. | Cucurmosin (CUS) | 1 | 27 | | [141, 142] |
| *Cucurbita moschata* Duchesne ex Poir. | Cucurmosin 2 | 1 | 27.2 | | [143] |
| *Cucurbita moschata* Duchesne ex Poir. | *Cucurbita moschata* RIP | 1 | 30.7 | | [144] |
| *Cucurbita pepo* L. | Pepocin | 1 | 26 | | [145] |
| *Cucurbita texana* (Scheele) A. Gray | Texanin | 1 | 29.7 | | [137] |
| *Dianthus barbatus* L. | Dianthin-29 | 1 | 29 | | [146] |
| *Dianthus caryophyllus* L. | Dianthin-30 | 1 | 29.5 | Yes | [147, 148] |
| *Dianthus caryophyllus* L. | Dianthin-32 | 1 | 31.7 | Yes | [147, 148] |
| *Dianthus sinensis* L. | *Dianthus sinensis* RIP (DsRIP) | 1 | 33.3 | | [149] |
| *Eranthis hyemalis* Salisb. | *Eranthis hyemalis* lectin (EHL) | 2 | 62 | | [150, 151] |
| *Gelonium multiflorum* A. Juss. | Gelonin (GAP31) | 1 | 31 | Yes | [152, 153] |
| *Gynostemma pentaphyllum* (Thunb.) Makino | Gynostemmin | 1 | 27 | | [144, 154] |
| *Gypsohila elegans* Bieb. | Gypsophilin | 1 | 28 | | [155] |
| *Hordeum vulgare* L. | Barley translation inhibitor (barley toxin I, BRIP) | 1 | 31 | Yes | [156] |
| *Hordeum vulgare* L. | Barley toxin II | 1 | 30 | Yes | [157] |
| *Hordeum vulgare* L. | Barley toxin III | 1 | 30 | | [157] |
| *Hordeum vulgare* L. | JIP60 (60 kDa jasmonate-induced protein) | 3 | 60 | | [158] |
| *Hura crepitans* L. | *Hura crepitans* RIP | 1 | 28 | | [105] |
| *Iris hollandica* L. | *Iris* agglutinin b (IRAb) | 2 | 65 | | [159] |
| *Iris hollandica* L. | *Iris* agglutinin r (IRAr) | 2 | 65 | | [159] |
| *Iris hollandica* L. | *Iris* RIP A1 (IRIP A1) | 1 | 30.9 | | [160] |
| *Iris hollandica* L. | *Iris* RIP A2 (IRIP A2) | 1 | 31 | | [160] |
| *Iris hollandica* L. | *Iris* RIP A3 (IRIP A3) | 1 | 30.9 | | [160] |
| *Jatropha curcas* L. | Curcin | 1 | 28.2 | Yes | [161, 162] |
| *Jatropha curcas* L. | Jc-SCRIP | 1 | 38.9 | | [163] |
| *Lagenaria siceraria* Molina. | Lagenin | 1 | 20 | | [164] |
| *Luffa acutangula* Roxb. | Luffaculin-1 | 1 | 28 | | [165] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Luffa acutangula* Roxb. | Luffaculin-2 | 1 | 28 | | [165] |
| *Luffa acutangula* Roxb. | Luffangulin | Small RIP | 6.5 | | [166] |
| *Luffa aegyptiaca* Mill. | Luffin-c | 1 | ND | | [167] |
| *Luffa aegyptiaca* Mill. | *Luffa* ribosomal inhibitory protein (LRIP) | 1 | 30 | Yes | [168] |
| *Luffa cylindrica* Mill. | Luffacylin | Small RIP | 7.8 | | [169] |
| *Luffa cylindrica* Mill. | Luffin-A (alpha-luffin) | 1 | 27 | Yes | [170, 171] |
| *Luffa cylindrica* Mill. | Luffin-B (beta-luffin) | 1 | 28 | Yes | [170] |
| *Luffa cylindrica* Mill. | Luffin-P1 | Small RIP | 5.2 | Yes | [172] |
| *Luffa cylindrica* Mill. | Luffin-S | Small RIP | 10 | | [173] |
| *Lychnis chalcedonica* L. | Lychnin | 1 | 26.1 | | [111, 174] |
| *Malania oleifera* Chun & S.K. Lee | Malanin | 2 | 61.9 | | [175] |
| *Manihot palmate* Mill. | Mapalmin | 1 | 32.3 | | [111] |
| *Manihot utilissima* Mill. | Manutin | 1 | 30.7 | | [176] |
| *Marah oreganus (Torr. ex S. Wats.) Howell* | MOR-I (*Marah oreganus* RIP-I) | 1 | 28 | | [177] |
| *Marah oreganus (Torr. ex S. Wats.) Howell* | MOR-II (*Marah oreganus* RIP-II) | 1 | 27.6 | | [177] |
| *Mesembryanthemum crystallinum* L. | RIP1 | 1 | 32.7 | | [178] |
| *Mirabilis expansa* Standl. | ME1 | 1 | 27 | | [179] |
| *Mirabilis expansa* Standl. | ME2 | 1 | 27.5 | | [179] |
| *Mirabilis jalapa* L. | *Mirabilis* antiviral protein (MAP) | 1 | 27.8 | | [180] |
| *Mirabilis jalapa* L. | MAP-2 | 1 | 30.4 | | [180] |
| *Mirabilis jalapa* L. | MAP-3 | 1 | 29.7 | | [180] |
| *Mirabilis jalapa* L. | MAP-4 | 1 | 29.3 | | [180] |
| *Momordica balsamina* L. | *Momordica balsamina* RIP-1 (MbRIP-1) | 1 | 30 | | [181] |
| *Momordica balsamina* L. | Momordin II | 1 | 32 | | [182] |
| *Momordica balsamina* L. | Balsamin | 1 | 28 | | [183] |
| *Momordica charantia* L. | Momordin (*Momordica charantia* inhibitor, momordin-a) | 1 | 23 | Yes | [184] |
| *Momordica charantia* L. | Alpha-momorcharin (alpha-MMc) | 1 | 29 | | [185, 186] |
| *Momordica charantia* L. | Beta-momorcharin (beta-MMc) | 1 | 28 | | [187, 188] |
| *Momordica charantia* L. | Gamma-momorcharin | Small RIP | 11.5 | | [189] |
| *Momordica charantia* L. | Delta-momorcharin | 1 | 30 | | [190] |
| *Momordica charantia* L. | Epsilon-momorcharin | 1 | 24 | | [190] |
| *Momordica charantia* L. | *Momordica charantia* lectin (MCL) | 2 | 130 | | [122] |
| *Momordica charantia* L. | Charantin | Small RIP | 9.7 | | [191] |
| *Momordica charantia* L. | Momordin I (*Momordica charanthia* inhibitor) | 1 | 31 | Yes | [147, 192] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Momordica cochinchinensis* Spreng | Momorcochin-S | 1 | 30 | Yes | [193] |
| *Momordica cochinchinensis* Spreng | Momorcochin | 1 | 32 | Yes | [194] |
| *Momordica cochinchinensis* Spreng | Cochinin B | 1 | 28 | | [195, 196] |
| *Momordica grosvenorii* Swingle | Momorgrosvin | 1 | 27.7 | | [197] |
| *Muscari armeniacum* Baker. | Musarmin-1 (MU-1) | 1 | 28.7 | | [198] |
| *Muscari armeniacum* Baker. | Musarmin-2 (MU-2) | 1 | 30 | | [198] |
| *Muscari armeniacum* Baker. | Musarmin-3 (MU-3) | 1 | 27.6 | | [198] |
| *Nicotiana tabacum* L. | Tobacco RIP (TRIP) | 1 | 26 | | [199] |
| *Nicotiana tabacum* L. | CIP31 | 1 | 31 | | [200] |
| *Oryza sativa* L. | *Oryza sativa* RIP | 1 | 33 | | [201] |
| *Oryza sativa* L. | *Oryza sativa* cultivar Kazemi RIP | 1 | 29 | | [202] |
| *Panax ginseng* L. | Panaxagin | RIP-like | 52 | | [203] |
| *Panax quinquefolium* L. | Quinqueginsin | RIP-like | 53 | | [204] |
| *Petrocoptis glaucifolia* (Lag.) Boiss. | Petroglaucin-1 | 1 | 26.7 | | [205] |
| *Petrocoptis glaucifolia* (Lag.) Boiss. | Petroglaucin-2 | 1 | 27.5 | | [206] |
| *Petrocoptis grandiflora* Rothm. | Petrograndin | 1 | 28.6 | | [205] |
| *Phoradendron californicum* Nutt. | *Phoradendron californicum* lectin (PCL) | 2 | 69 | | [207] |
| *Phytolacca americana* L. | PAP (pokeweed antiviral protein, *Phytolacca* antiviral protein) | 1 | 29 | Yes | [208, 209] |
| *Phytolacca americana* L. | PAP II (pokeweed antiviral protein II) | 1 | 30 | Yes | [209] |
| *Phytolacca americana* L. | PAP III (pokeweed antiviral protein III) | 1 | 30 | | [210, 211] |
| *Phytolacca americana* L. | PAP-S | 1 | 30 | Yes | [212] |
| *Phytolacca americana* L. | PAP-C | 1 | 29 | | [213] |
| *Phytolacca americana* L. | PAP-R | 1 | 29.8 | | [111] |
| *Phytolacca americana* L. | PAP-H | 1 | 29.5 | | [214] |
| *Phytolacca dioica* L. | PD-S1 (*Phytolacca dioica* RIP 1) | 1 | 30 | | [215] |
| *Phytolacca dioica* L. | PD-S2 (*Phytolacca dioica* RIP 2) | 1 | 29.6 | Yes | [215, 216] |
| *Phytolacca dioica* L. | PD-S3 (*Phytolacca dioica* RIP 3) | 1 | 30 | | [215] |
| *Phytolacca dioica* L. | PD-L1 | 1 | 32.7 | | [217, 218] |
| *Phytolacca dioica* L. | PD-L2 | 1 | 31.5 | | [217, 218] |
| *Phytolacca dioica* L. | PD-L3 | 1 | 30.4 | | [217, 218] |
| *Phytolacca dioica* L. | PD-L4 | 1 | 29.2 | | [217, 218] |
| *Phytolacca dioica* L. | Dioicin 1 | 1 | 30 | | [219, 220] |
| *Phytolacca dioica* L. | Dioicin 2 | 1 | 29.9 | | [219, 220] |
| *Phytolacca dodecandra* L'Herrit | Dodecandrin | 1 | 29 | | [221] |
| *Phytolacca heterotepala* H. Walter | Heterotepalin-4 (Mexican pokeweed RIP-4, *Phytolacca heterotepala* anti-viral protein PAP) | 1 | 29.3 | | [222] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Phytolacca heterotepala* H. Walter | Heterotepalin-5b (Mexican pokeweed RIP-5b) | 1 | 30.5 | | [222] |
| *Phytolacca insularis* Nakai | *Phytolacca insularis* antiviral protein (PIP, insularin) | 1 | 35 | | [223] |
| *Phytolacca insularis* Nakai | *Phytolacca insularis* antiviral protein 2 (PIP2) | 1 | 35.7 | | [224] |
| *Pisum sativum* L. | Alpha-pisavin | 1 | 20.5 | | [225] |
| *Pisum sativum* L. | Beta-pisavin | 1 | 18.7 | | [225] |
| *Pisum sativum* L. | Sativin | 1 | 38 | | [226] |
| *Polygonatum multiflorum* Kunth. | *Polygonatum multiflorum* RIP monomer (PMRIPm) | 2 | 60 | | [227] |
| *Polygonatum multiflorum* Kunth. | *Polygonatum multiflorum* RIP tetramer (PMRIPt) | 2 | 240 | | [227] |
| *Ricinus communis* L. | Ricin | 2 | 62 | Yes | [228] |
| *Ricinus communis* L. | Ricin 1 | 2 | 64 | | [229] |
| *Ricinus communis* L. | Ricin 2 | 2 | 67 | | [229] |
| *Ricinus communis* L. | Ricin 3 | 2 | 66 | | [229] |
| *Ricinus communis* L. | Ricin D | 2 | 60 | | [230] |
| *Ricinus communis* L. | Ricin E | 2 | 60 | | [231] |
| *Ricinus communis* L. | *Ricinus* agglutinin (RCA120) | 2 | 120 | | [97] |
| *Ricinus communis* L. | *Ricinus* agglutinin 1 (RCA1) | 2 | 134 | | [229] |
| *Ricinus communis* L. | *Ricinus* agglutinin 2 (RCA2) | 2 | 140 | | [229] |
| *Ricinus sanguineus* Hort. ex Groenland | Ricin R2 | 2 | 63.1 | | [232] |
| *Ricinus sanguineus* Hort. ex Groenland | Ricin R11 | 2 | 57.8 | | [232] |
| *Ricinus sanguineus* Hort. ex Groenland | Ricin R12 | 2 | 62.2 | | [232] |
| *Ricinus sanguineus* Hort. ex Groenland | *Ricinus sanguineus* agglutinin | 2 | 120 | | [233] |
| *Sambucus ebulus* L. | Ebulin r | 2 | 56 | | [234] |
| *Sambucus ebulus* L. | Ebulin I (ebulin 1) | 2 | 56 | Yes | [235] |
| *Sambucus ebulus* L. | Alpha-ebulitin | 1 | 32 | | [236] |
| *Sambucus ebulus* L. | Beta-ebulitin | 1 | 29 | | [236] |
| *Sambucus ebulus* L. | Gamma-ebulitin | 1 | 29 | | [236] |
| *Sambucus nigra* L. | Basic nigrin b | 2 | 63.5 | | [237] |
| *Sambucus nigra* L. | Nigrin b | 2 | 58 | Yes | [238] |
| *Sambucus nigra* L. | Nigritin f1 | 1 | 24.1 | | [239] |
| *Sambucus nigra* L. | Nigritin f2 | 1 | 23.6 | | [239] |
| *Sambucus nigra* L. | *Sambucus nigra* agglutinin I (SNAI) | 2 | 140 | | [240] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Sambucus nigra* L. | SNLRP | 2 | 60 - 62 | | [241] |
| *Sambucus racemosa* L. | Basic racemosin b | 2 | 58 | | [242] |
| *Sambucus sieboldiana* L. | Sieboldin-b | 2 | 59.4 | | [243] |
| *Saponaria ocymoides* L. | Ocymoidine | 1 | 30.2 | Yes | [244] |
| *Saponaria officinalis* L. | Saporin-6 | 1 | 29.5 | Yes | [105, 245] |
| *Saponaria officinalis* L. | Saporin-9 | 1 | 29.5 | | [105] |
| *Saponaria officinalis* L. | Saporin-L1 | 1 | 31.6 | Yes | [246] |
| *Saponaria officinalis* L. | Saporin-L2 | 1 | 31.6 | | [246] |
| *Saponaria officinalis* L. | Saporin-R1 | 1 | 30.2 | | [246] |
| *Saponaria officinalis* L. | Saporin-R2 | 1 | 30.9 | | [246] |
| *Saponaria officinalis* L. | Saporin-R3 | 1 | 30.9 | | [246] |
| *Saponaria officinalis* L. | Saporin-S5 | 1 | 30.9 | | [246] |
| *Saponaria officinalis* L. | Saporin-S6 | 1 | 31.6 | Yes | [246] |
| *Saponaria officinalis* L. | Saporin-S8 | 1 | 29.5 | | [246] |
| *Saponaria officinalis* L. | Saporin-S9 | 1 | 29.5 | | [246] |
| *Secale cereale* L. | *Secale cereale* RIP | 1 | 31 | | [247] |
| *Sechium edule* (Jacq.) Sw. | Sechiumin | 1 | 27 | | [248] |
| *Spinacia oleracea* L. | *Spinacia oleracea* RIP1 (SoRIP1, BP31) | 1 | 31 | | [249] |
| *Spinacia oleracea* L. | *Spinacia oleracea* RIP2 (SoRIP2) | 1 | 29 | | [249] |
| *Stellaria aquatica* Scop. | Stellarin | 1 | ND | | [250] |
| *Stellaria media* (L.) Vill. | RIP Q3 | 1 | 28.2 | | [251] |
| *Trichosanthes anguina* L. | Trichoanguin | 1 | 35 | | [252] |
| *Trichosanthes cucumerina* Wall. | *Trichosanthes cucumerina* seed lectin (TCSL) | RIP-like | 69 | | [253] |
| *Trichosanthes cucumeroides* Maxim. | Beta-trichosanthin | 1 | 28 | | [254] |
| *Trichosanthes dioica* Roxb. | *Trichosanthes dioica* seed lectin (TDSL) | RIP-like | 55 | | [255] |
| *Trichosanthes kirilowii* Maxim. | Alpha-kirilowin | 1 | 28.8 | | [256] |
| *Trichosanthes kirilowii* Maxim. | Beta-kirilowin | 1 | 27.5 | | [257] |
| *Trichosanthes kirilowii* Maxim. | Trichosanthin (TCS) | 1 | 25 - 26 | Yes | [258] |
| *Trichosanthes kirilowii* Maxim. | TAP-29 (*Trichosanthes* anti-HIV protein 29 kDa) | 1 | 29 | | [259] |
| *Trichosanthes kirilowii* Maxim. | Trichobitacin | 1 | 27.2 | | [260, 261] |
| *Trichosanthes kirilowii* Maxim. | S-Trichokirin | Small RIP | 8 | | [262] |
| *Trichosanthes kirilowii* Maxim. | Trichokirin-S1 | Small RIP | 11.4 | | [263] |
| *Trichosanthes kirilowii* Maxim. | Alpha-trichosanthin | 1 | 31.7 | | [264] |
| *Trichosanthes kirilowii* Maxim. | Karasurin-A | 1 | 27.1 | | [265, 266] |
| *Trichosanthes kirilowii* Maxim. | Karasurin-B | 1 | 27.2 | | [267] |
| *Trichosanthes kirilowii* Maxim. | Karasurin-C | 1 | 27.4 | | [267] |

**(Table 1) Contd….**

| Plant | RIP | Type | Ma (kDa) | Immunotoxins | Ref. |
|---|---|---|---|---|---|
| *Trichosanthes kirilowii* Maxim. | Trichosanthrip | Small RIP | 11 | | [268] |
| *Trichosanthes kirilowii* Maxim. | Trichomislin | 1 | 27.2 | | [269] |
| *Trichosanthes kirilowii* Maxim. | Trichokirin | 1 | 27 | Yes | [270] |
| *Trichosanthes lepiniate* Maxim. | Trichomaglin | 1 | 24.7 | | [271] |
| *Trichosanthes sp. Bac Kan 8-98* | Trichobakin | 1 | 27 | | [272] |
| *Triticum aestivum* L. | Tritin | 1 | 30 | | [273] |
| *Vaccaria pyramidata* Medik. | Pyramidatine | 1 | 28 | Yes | [244] |
| *Viscum album* L. | Viscumin (mistletoe lectin I) | 2 | 60 | Yes | [274] |
| *Viscum articulatum* Burm. F. | Articulatin-D | 2 | 66 | | [275] |
| *Ximenia americana* L. | Riproximin | 2 | 63 | | [276] |
| *Zea mays* L. | Maize seed RIP (b-32, corn RIP) | 1 | 32.4 | | [277] |
| *Zea mais* L. | Maize proRIP | 3 | 34 | | [278] |

it is transported to the Golgi-apparatus by retrograde transport and finally reaches the endoplasmic reticulum (ER). Within the ER the disulfide bonds are cleaved by thioredoxin reductases and disulfide isomerases [9, 10]. The enzymatically active A chain is released and partially unfolded during this process [11]. To facilitate its entry into the cytosol, the A chain exploits a mechanism, which is known as ER-associated degradation (ERAD). ERAD is a natural mechanism for maintaining the homeostasis of the ER [12]. Proteins that are misfolded and thus non-functional are designated for proteasome degradation within the cytosol. The transport of the partially unfolded A chain is mediated by the translocon Sec61p [13] and the ER degradation-enhancing α-mannosidase-like protein 1 [14]. One of the most important factors for the cytosolic delivery is the recognition of the A chain as a substrate for the ERAD system. This is achieved by disguising the A chain as a misfolded protein. After reaching the cytosol the partially unfolded A chain is fully refolded to regain the conformational integrity as an enzymatically active form. This is facilitated by the chaperons Hsc70 and Hsp90 [15]. Genetic interaction maps indicate the involvement of a number of different factors responsible for modulating the ricin trafficking [16]. The cytosolic delivery of the A chain marks the end of a highly efficient molecular strategy that ricin adopts in order to direct the catalytic domain to the ribosomes.

As mentioned before, a common feature of all the RIPs is their ability to depurinate the rRNA by releasing an adenine residue at their α-sarcin/ricin loop. This results in an irreversible inhibition of protein synthesis facilitated by the prevention of eukaryotic elongation factor binding [17]. According to the protein data bank (PDB), RIPs belong to a group of rRNA *N*-glycosidases (EC 3.2.2.22) that hydrolyze the *N*-glycosidic bonds at the position 4324 on the 28S rRNA. The bond between the N9 of adenine and the C1 of ribose is hydrolyzed by a concerted action of an arginine at position 180 (R180) and a glutaminic acid at position 177 (E177). E177 is stabilized at a cationic oxocarbenium ribose transition state and R180 is responsible for activating water. This facilitates the nucleophilic attack on the C1 of the oxocarbenium intermediate resulting in the release of adenine [18]. Mutants lacking E177 and R180 are also devoid of the *N*-glycosidase activity [19]. Recent studies suggest that the action of RIPs on ribosomes depends on the ribosomal stalk, which is a network of different proteins that recruit translational factors to the ribosomes [20]. After gaining access to their substrate, RIPs act as toxic agents. It is further hypothesized that only one internalized molecule is sufficient to kill one cell. From an evolutionary point of view, it has been suggested that the B chain of ricin was generated by a lateral gene transfer from a bacteria.

Contrasting to type 2 RIPs, type 1 RIPs are less toxic [21] and consist of only the A chain (*N*-glycosidase), which lacks any specific cell binding properties. The low cytotoxicity of type 1 RIPs is generally attributed to an inefficient endocytosis. However, based on some other reports [22] and our own experiments (Fig. **1**), it is admissible that type 1 RIPs are effectively internalized. The major problem restricting their efficacy is the inefficient endosomal release.

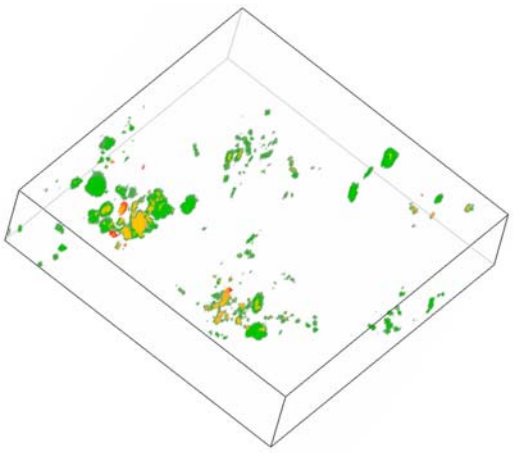

**Fig. (1).** Three-dimensional depiction (z-stacks) of the endosomal network of ECV-304 cells loaded with $^{Alexa}$saporin. ECV-304 cells were challenged for 3 h with 1 μM Alexa-Fluor 488 labeled saporin (type I RIP from *Saponaria officinalis* L.). Cells were co-incubated with pH rodo™ Red Dextran, a marker for endo/lysosomes and analyzed by confocal live cell imaging. Depicted is the endo/lysosomal network of one living ECV-304 cell. Green: $^{Alexa}$saporin in celular vesicles, red: pHrodo™ Red Dextran in endosomes/lysosomes, yellow: co-localization of $^{Alexa}$saporin and pHrodo™ Red Dextran in endosomes/lysosomes. The figure illustrates the fact that saporin is internalized and trapped in to the endosomal vesicles, thereafter it is degraded by the endo/lysosomal degradation.

The exact mechanism of the internalization of type 1 RIPs is not deciphered so far. Previous studies indicate towards a receptor-mediated endocytosis of type I RIPs by low density lipoprotein (LDL) receptors [23-26]. Contrastingly, some other results confirm a receptor independent endocytosis [22]. However, the exertion of toxic effects appears to be independent of the internalization mechanism. The toxicity determining factor is the ability of type 1 RIPs to cross the endo/lysosomal membrane. Since type 1 RIPs do not contain any transduction domains facilitating the endo/lysosomal escape into the cytosol, they are less cytotoxic. Upon endocytosis, type 1 RIPs are delivered into the cellular compartments that are positive for lysobisphosphatidic acid (LBPA) (a specific eukaryotic phospholipid marker for late endosomes) and the lysosomal-associated membrane proteins LAMP1 and LAMP2 [22, 27]. Type I RIPs are thereafter degraded within the lysosomes [5].

**Immunotoxins and Targeted Toxins**

Immunotoxins as per definition are conjugates of cell binding antibodies and the complete type 1/2 RIP or the A chain of a type 2 RIP [6]. In all the reported cases, the complete type 2 RIP has a very high cytotoxic effect when conjugated to the antibody. Nonetheless, there is an increased side effect due to the off-target binding of the B chain. To circumvent this, a lot of alternative strategies including but not limited to the use of high concentrations of free galactose or lactose as competitive binders have been tested. Another alternative in overcoming this problem has been the use of steric hindrance [28]. Coupling of an antibody or its fragment to the isolated A chain *via* disulfide linkage appears to be the most effective strategy. RIPs lack thiol groups for a disulfide linkage and it is necessary to synthetically introduce it. Alternatively, other linkages such as maleimide linkage have also been attempted but are not successful, mainly due to the inability of cellular enzymes to reductively cleave the bonds [29].

Another important term for the fusion proteins comprising of toxins is targeted toxin. It is a term which coherently finds usage in the literature to define a generic name for immunotoxins. In general, targeted toxins comprise of tumor specific ligands coupled to polypeptide toxins. They constitute a class of cancer therapeutics that leads to the death of cancer cells. They mainly act by the inactivation of cytosolic protein synthesis and induction of programmed cell death [3]. Immunotoxins are *per se*, restricted to an antibody or antibody fragment as the targeting moiety whereas, targeted toxins form a larger domain including the use of antibodies, small antibody fragments, growth factors, cytokines or small peptides as targeting moieties. Thus, immunotoxins form a smaller subset of targeted toxins as a classification in general.

These targeted toxins can either be prepared by chemical conjugation as described above, or they can be produced recombinantly as a fusion protein that is expressed in cells [6]. Within the past two decades, significant progress has been made towards proper identification of the appropriate cellular target for toxins with target specificity. Moreover, tremendous progress made in the field of genetic engineering and a better understanding of receptor physiology coupled with the single molecule tracking modality have led to an exponential growth in the scientific output as far as targeted toxins are concerned. This is further evidenced by an increased number of clinical trials which are being conducted on targeted toxins, with many of them in Phase 3 [30, 31].

Plant RIPs constitute a major portion of the therapies with targeted toxins, and although there is additional literature available on bacterial and human toxins, plant RIPs generate a lot of scientific interest. As listed in Table **2**, there are more than 450 targeted toxins described, which comprise of plant RIPs as a toxic moiety. Amongst various RIPs the leading toxin components are ricin A chain from *Ricinus communis* L., saporin from *Saponaria officinalis* L. and gelonin from *Gelonium multiflorum* A. Juss. A lot of different targeting ligands have been successfully coupled to these toxins and have demonstrated high specificity in *in vitro* and preclinical evaluations. The ligand, apart from providing selectivity, also helps in cellular internalization of the toxin. There are a number of aspects associated with the internalization and trafficking of toxins. When the toxins are transformed into targeted toxins, there are numerous critical elements deciding their fate *in vitro* and *in vivo*; these events are discussed in detail hereafter.

**Antigen Selection and Efficiency of Internalization**

The analysis of the expression pattern of tumor-associated surface antigens and the knowledge about their ability to promote or modulate the tumor growth are critical for the identification of novel targets for targeted anti-tumor therapies. For the development of monoclonal antibodies (mAbs) or targeted toxins, it is essential to determine, whether a particular surface antigen undergoes an accelerated internalization or not (Fig. **2**). There is a variety of cancer-associated antigens that are being targeted by mAbs [32, 33]. For mAbs that mediate their efficacy in part by interaction with natural killer cells (NK) (antibody dependent cellular cytotoxicity, ADCC), it is important to select antigens, which do not undergo rapid down-regulation after binding. This is a feature contrasting the modality of targeted toxins, where it is desirable to select antigens that show enhanced endocytosis after ligand binding [34]. This facilitates a rapid delivery of the toxin into the cancer cells.

The receptor that is being addressed by the targeted toxin should be over-expressed on the tumor cell surface compared to the normal tissue. A considerable number of receptors [35] have been addressed to date, amongst them are the cytokine receptors [36], tumor necrosis factor receptor, growth factor receptors [37, 38] and cluster of differentiation CD22 [39], CD25 [40] and CD30 [41]. Contrasting to the numerous advantages listed above, a drawback of antibody-based targeted toxins is their limited ability to induce the effector functionalities of the naked antibodies. It is in fact a predominant basis for the concept of targeted toxins, wherein it is envisaged to outweigh the biological functionalities of the monoclonal antibodies by conjugating them to bacterial toxins such as *Pseudomonas* exotoxin from *Pseudomonas aeruginosa* [42] or plant toxins such as saporin from *Saponaria officinalis* L.

**Release of Targeted Toxins into the Cytosol and their Lysosomal Degradation**

Once internalized, the targeted toxin is delivered into early endosomes. Early endosomes are part of the endosomal transport system, which is an intracellular vesicular and tubular compartment surrounded by cytosol. Within early endosomes, endocytosed ligands (targeted toxins) are either designated for recycling [43, 44] or they are further transported into late endosomes, and finally lysosomes for degradation. Since targeted toxins exert their antitumoral efficacy only in the cytosol, it is a vital prerequisite for their efficacy that they are able to escape from the endosomal network into the cytosol. Targeted toxins fused to truncated variants of bacterial toxins such as diphtheria toxin (DT) from *Corynebacterium diphtheriae* utilize the native T-domain of DT to escape from early endosomes into the cytosol [42, 45, 46] while other targeted toxins employ a KDEL-like motive of their toxin moieties, which in turn facilitate their retrograde delivery into the ER and thereafter their transport to the cytosol [47]. However, plant-derived toxins such as saporin and gelonin or the A chain of the type 2 RIP ricin does not comprise of such translocation domains. It can be therefore anticipated that the cytosolic delivery of type 1 RIP-based targeted toxins is attenuated, compared to appropriate bacterial counterparts. However, comparative studies in this regard have not been undertaken so far.

Several strategies such as photochemical internalization [48], pore formation by listeriolysin O from *Listeria monocytogenes* [37], cell penetration by protein transduction domains [49], the use of lysosomotropic agents like chloroquine [50] or the use of triterpe-

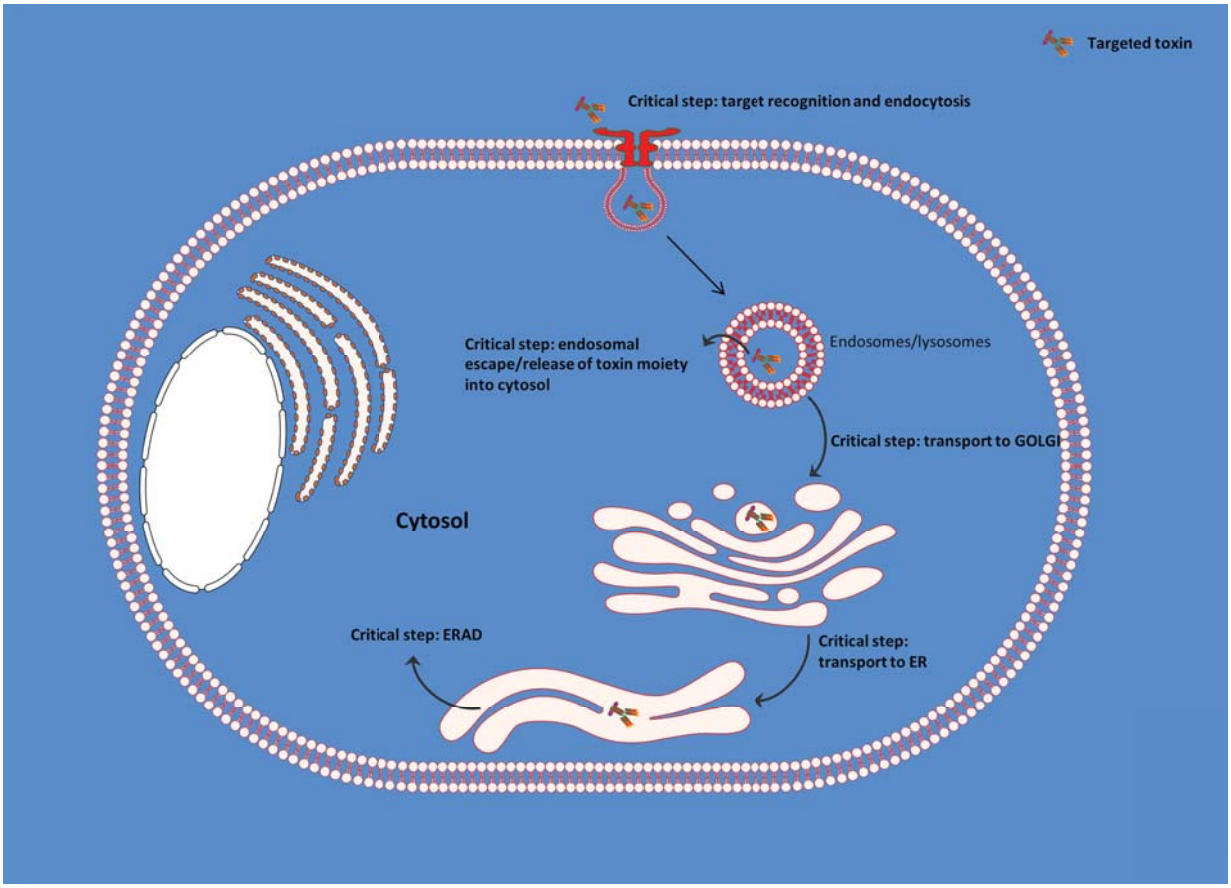


**Fig. (2).** An overview of the steps required for the recognition and internalization of the targeted toxin in the tumor cells. The critical step of target recognition determines the specificity, thereafter the celular machinery takes over and in the ideal case the toxin escapes from the endosomal membrane thus inactivating the ribosomes *via N*-glycosidase activity.

noidal saponins from *Saponaria officinalis* L. and *Gypsophila paniculata* L. [51, 52] have been developed to facilitate the escape of targeted toxins from endosomal vesicles (a schematic overview on the obstacles for the cytosolic delivery of targeted toxins is depicted below above). All these methods prevent the lysosomal degradation of targeted toxins by mediating their endosomal escape into the cytosol. This results in a significant augmentation of the antitumoral efficacy of the targeted toxin.

Lysosomal degradation is one of the main issues in targeted tumor therapies [53]. It may be compensated by increasing the dosage of the targeted toxins, however, this does promote undesirable side effects. As mentioned above, lysosomal degradation can be outweighed by combination strategies that mediate the endosomal escape of targeted toxins. The generation of modified targeted toxins that are resistant against lysosomal degradation is a further attractive strategy to increase the efficacy of targeted toxins [54].

## Advancement in the Use of RIPs as Therapeutic Agent

Initially, targeted toxins were constructed with native ricin and were tested *in vitro* in the presence of high concentrations of lactose which prevented the non-specific binding of ricin B-chain. Blocking of the oligosaccharide binding sites was used to prevent off-target ricin uptake and provided the possibility of applying the immunotoxins *in vivo* [55]. The separation of RTA and ricin B-chain by chemical reduction allowed conjugation of the antibody to the catalytic subunit, mainly through cross-linkers containing a disulfide bond. Despite the high yield and good stability of these targeted toxins, one of the main disadvantages for them was a heterogeneous composition [28]. Furthermore, it is well known that the glycosylated residues of RTA also facilitate non-specific uptake by macrophages. Therefore, in order to prevent the non-specific uptake, RTA was submitted to a process of deglycosylation before conjugation to the antibody and formation of the immunotoxin [56].

The advancement of recombinant tools has led to a rather ubiquitous utilization of these techniques for the production of toxins. For generating these targeted toxins, the gene portion encoding the antigen-binding fragments of an antibody (Fab or Fv) is generally coupled to the gene encoding for native catalytic domain. In another case it may be linked to the mutated version of the toxin. Once the construct is available it can be proliferated in any expression system such as bacteria, yeast or algae [57, 58]. The first generated recombinant immunotoxins were mostly formed using the single-chain variable fragments (scFvs), thereafter they were substituted by disulfide-stabilized Fvs (dsFvs). The scFvs have a peptide linker compared to the disulfide bridge in dsFvs which makes the conformation more stable.

## Future Perspectives and Opinions on Targeted Toxins

Cancer is an expended burden in an ageing population. In the fight against this complex phenomenon, it would be a misjudgment to believe that one day a single strategy such as the use of targeted toxins will be able to defeat this disease. Thus, different complementary strategies are required to overcome all the hurdles that impede recovery. Surgical intervention, chemotherapy and radiation constitute the traditional troika of cancer therapies that are used as commonly for a wide variety of tumors.

**Table 2. A comprehensive list of all the targeted toxins based on plant RIPs investigated so far.**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Abrin | Abrin-9.2.27 | mAb (9.2.27) | Melanoma-associated antigen (p250) | Melanoma | Yes | Yes | | [279, 280] |
| Abrin | Abrin-NR-ML-05 | mAb (NR-ML-05) | Melanoma-associated antigen (p250) | Melanoma | Yes | | | [281] |
| Abrin A-chain | Fib 75-abrin A chain | mAb (LICR-LOND Fib 75) | Bladder cancer antigen | EJ bladder cancer | Yes | Yes | | [282-284] |
| Abrin A-chain | C27-Abrin A chain (MAAC) | mAb (C27) | Carcinoembryonic antigen (CEA) | Colorectal cancer | Yes | Yes | | [285] |
| Abrin A-chain | Anti-Thy 1.1-Abrin A-chain | mAb (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | AKR-A lymphoma | Yes | Yes | | [286] |
| Abrin A-chain | Anti-Hepatoma-associated Antigen-Abrin A-chain | mAb (anti-hepatoma-associated antigen L10 190 kDa glycoprotein) | Hepatoma-associated antigen L10 190 kDa glycoprotein | Hepatocarcinoma | Yes | | | [287] |
| Abrin A-chain | ITA | IgG (anti-Trypanosoma cruzi surface antigens) | Trypanosoma cruzi surface antigens | *Trypanosoma cruzi* | Yes | | | [288] |
| Abrin A-chain | F1G4-rABRa-A | mAb (F1G4) | Gonadotropin releasing hormone (GnRH) receptor | Breast cancer, hepatocarcinoma | Yes | | | [289] |
| Abrin A-chain | SWA11-SPDB-abrin A | mAb (SWA11) | CD24 | SCLC | Yes | | | [290] |
| Abrin A-chain | ABRaA-$VEGF_{121}$ | $VEGF_{121}$ | VEGFR-2 | Melanoma | Yes | Yes | | [291] |
| Abrin variant | Tfn-abrin variant | Human diferric transferrin (Tfn) | TfR | Glioblastoma multiforme, melanoma | Yes | | | [292] |
| Barley toxin I | H65-MM-rBRIP | mAb (H65) | CD5 | ALL | Yes | | | [293] |
| Barley toxin I | 4A2-MM-rBRIP | mAb (4A2) | CD7 | ALL | Yes | | | [293] |
| Barley toxin I | Anti-melanoma-BRIP | mAb (anti-melanoma) | Melanoma antigen | Melanoma | Yes | | | [294] |
| Barley toxin II | 5E9C11-Barley toxin II | mAb (HB21) (5E9) | TfR | Colon cancer | Yes | | | [157] |
| Bouganin | Anti-CD80/bouganin (M24-bouganin) | mAb (M24) | CD80 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | | | [295] |
| Bouganin | Anti-CD86/bouganin | mAb (anti-CD86) (1G10) | CD86 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | | | [295] |
| deBouganin | VB6-845 | Fab (4D5MOCB) | EpCAM | Solid tumors of epithelial origin | Yes | Yes | Phase I | [296, 297] |
| Bryodin-1 | OX7-bryodin | mAb (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | AKR-A lymphoma | Yes | | | [298] |
| Bryodin-1 | BD1-G28-5 sFv | scFv (G28-5) | CD40 | B-cell non-Hodgkin's lymphoma, multiple myeloma | Yes | | | [299, 300] |
| Bryodin-1 | chiBR96-BD-1 | scFv (BR96) | $Le^y$ antigen | Breast cancer | Yes | | | [301] |
| Bryodin-1 | Anti-epithelial antigen-bryodin | mAb (anti-epithelial antigen) | Epithelial antigen | Colon cancer, epidermoid carcinoma | Yes | | | [302] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Bryodin-1 | $F(ab')_2$-bryodin/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Bryodin-2 | chiBR96-BD-2 | scFv (BR96) | $Le^y$ antigen | Breast cancer | Yes | | | [301] |
| Bryodin-2 | HB21-bryodin-II | mAb (HB21) (5E9) | TfR | Breast cancer | Yes | | | [304] |
| Colocin 1 | Anti-epithelial antigen-colocin 1 | mAb (anti-epithelial antigen) | Epithelial antigen | Colon cancer, epidermoid carcinoma | Yes | | | [302] |
| Curcin | Curcin-TfRBP9 | TfRBP9 [transferrin receptor (TfR) binding peptide] | TfR | Hepatocellular carcinoma | Yes | | | [305] |
| Dianthin 30 | BerH2-dianthin | mAb (Ber-H2) | CD30 | Lymphoblastoid, Hodgkin's lymphoma | Yes | | | [306, 307] |
| Dianthin 30 | Dianthin-EGF | EGF | EGFR | EGFR overexpressing cells | Yes | | | [84, 308] |
| Dianthin 30 | Tfn-dianthin | Transferrin | TfR | T-cell leukemia | Yes | | | [309] |
| Dianthin 32 | $F(ab')_2$-dianthin 32/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Ebulin l | Ebulin l-transferrin | Transferrin | TfR | TfR-over-expressing cancer cells | Yes | | | [310] |
| Ebulin l | 44G4-ebulin | mAb (44G4) | CD105 (endoglin) | Tumor neovasculature | Yes | | | [311] |
| Gelonin | Fib 75-gelonin | mAb (LICR-LOND Fib 75) | Bladder cancer antigen | EJ bladder cancer | Yes | Yes | | [284, 312] |
| Gelonin | Anti-CD86/gelonin (αCD86-gelonin) | mAb (anti-CD86) (1G10) | CD86 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | Yes | | [295, 313] |
| Gelonin | Anti-CD80/gelonin (M24-gelonin) | mAb (M24) | CD80 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | | | [295] |
| Gelonin | αCD80-gelonin | mAb (B5B) | CD80 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | | | [313] |
| Gelonin | J5/gelonin | mAb (J5) | CD10 (CALLA) | Lymphoma | Yes | | | [314] |
| Gelonin | I-2/gelonin | mAb (I-2) | Ia antigen | Lymphoma | Yes | | | [314] |
| Gelonin | J30/gelonin | mAb (J30) | gp26 cell surface glycoprotein | Lymphoma | Yes | | | [314] |
| Gelonin | BerH2-gelonin | mAb (Ber-H2) | CD30 | Hodgkin's lymphoma | Yes | | | [307] |
| Gelonin | NDA4-gelonin | mAb (NDA4) | NDA4 antigen | EBV-transformed lymphoblastoid, gibbon MLA leukemia | Yes | | | [315] |
| Gelonin | HB21-gelonin (5E9-gelonin) | mAb (HB21) (5E9) | TfR | Colon cancer, Burkitt's lymphoma | Yes | Yes | | [157, 316] |
| Gelonin | OKT9-gelonin | mAb (OKT9) | TfR | Cervical cancer | Yes | | | [317] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Gelonin | Lym-I-gelonin | mAb (Lym-1) | HLA-DR | Burkitt's lymphoma cells | Yes | | | [318] |
| Gelonin | B4G7-gelonin | mAb (B4G7) | EGFR | Lung cancer | Yes | Yes | | [319] |
| Gelonin | 80G-gelonin | mAb (80G) | Alpha-fetoprotein | Hepatoma | Yes | Yes | | [320] |
| Gelonin | ZME-gelonin | mAb (ZME-018) | Proteoglycan, p250 | Melanoma | Yes | Yes | | [321, 322] |
| Gelonin | Gelonin-9.2.27 | mAb (9.2.27) | Melanoma-associated antigen (p250) | Melanoma | Yes | Yes | | [280] |
| Gelonin | AChR-gelonin | AChR (nicotinic acetyl-choline receptor) | IgG (anti-AChR) | Experimental auto-immune myasthenia gravis (EAMG) | Yes | Yes | | [323] |
| Gelonin | 38.13-gelonin | mAb (38.13) | TH ceramide (Pk antigen) | Burkitt's lymphoma | Yes | | | [324] |
| Gelonin | Anti-T11-gelonin | mAb (OKT11) | CD2 | T cells | Yes | Yes | | [325, 326] |
| Gelonin | Tf-gelonin | Transferrin | TfR | Malaria (*Plasmodium falciparum*) | Yes | | | [327] |
| Gelonin | AR3-gelonin | mAb (AR3) | CAR-3 | Gastric cancer | Yes | Yes | | [328] |
| Gelonin | 15A8-gelonin | mAb (15A8) | Breast cancer antigen | Breast cancer, cervi-cal cancer | Yes | | | [329] |
| Gelonin | HB5-gelonin | mAb (HB5) | Cd3 receptor | EBV infection | Yes | | | [330] |
| Gelonin | Anti-Lyt 2.2-gelonin | mAb (anti-Lyt 2.2) (19/178$C_1$) | Lyt2.2 | T-cell lymphoma | Yes | | | [331] |
| Gelonin | Anti-Thy 1.2-gelonin | mAb (anti-Thy 1.2) (AT15E) | CD90.2 (Thy 1.2) | T-cell lymphoma | Yes | | | [331] |
| Gelonin | Anti-Thy 1-gelonin | mAb (anti-Thy 1) (M549) | CD90 (Thy 1.1 and 1.2) | Leukemia | Yes | Yes | | [332] |
| Gelonin | LG 2/72-gelonin | mAb (LG 2/72) | HLA-DR | Lymphoma | Yes | | | [331] |
| Gelonin | Anti-MCMV-gelonin | IgG (anti-MCMV) | MCMV antigen (murine cytomega-lovirus antigen) | CMV infection | Yes | | | [333] |
| Gelonin | Anti-HCMV-gelonin | IgG (anti-HCMV) | HCMV antigen (hu-man cytomegalovirus antigen) | CMV infection | Yes | | | [333] |
| Gelonin | Anti-JL1-gelonin | mAb (anti-JL1) | JL1 | Leukemia | Yes | | | [334] |
| Gelonin | oLH-gelonin (lutropin-SS-gelonin) | Ovine luteinizing hor-mone (oLH) | Ovine LH receptor | Leydig cell tumor (testicular cancer) | Yes | | | [335] |
| Gelonin | hCG-gelonin | Human chorionic go-nadotropin (hCG) | LH receptor | Leydig cell tumor (testicular cancer) | Yes | | | [335] |
| Gelonin | Gelonin-gp330 | gp330 (renal brush border antigen) | Anti-gp330 Ig | Heymann's nephritis | Yes | Yes | | [336] |
| Gelonin | Anti-PCV-gelonin | IgG (anti-PCV) | Pichinde virus (PCV) | Pichinde virus (PCV) | Yes | | | [337] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Gelonin | PC4.9A6-gelonin | mAb (PC4.9A6) | Pichinde virus (PCV) | Pichinde virus (PCV) | Yes | | | [337] |
| Gelonin | 14G2a-gelonin | mAb (14G2a) | Disialoganglioside GD2 | Neuroblastoma, melanoma | Yes | | | [338] |
| Gelonin | MSN-1-gelonin | mAb (MSN-1) | Endometrial adeno-carcinoma antigen | Endometrial adeno-carcinoma | Yes | Yes | | [339] |
| Gelonin | $F(ab')_2$-gelonin/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Gelonin | H65-gelonin | mAb (H65) | CD5 | T-cell ALL | Yes | Yes | | [340] |
| Gelonin | BACH-250/rGel | mAb (BACH-250) | HER2 | Breast cancer | Yes | Yes | | [341] |
| Gelonin | TAB-250/rGel | mAb (TAB-250) | HER2 | Breast cancer | Yes | Yes | | [341] |
| Gelonin | $VEGF_{121}$/rGel | $VEGF_{121}$ | KDR Flk-1 receptor | Tumor neovascula-ture, melanoma, prostate cancer | Yes | Yes | | [342] |
| Gelonin | HuM195/rGel | mAb (HuM-195) | CD33 | AML, CML, myelo-dysplastic syndrome | Yes | Yes | Phase I | [343-346] |
| Gelonin | MEL scFv-rGel | scFv (MEL) | gp240 | Melanoma, brain cancer, lobular breast cancer | Yes | Yes | | [347] |
| Gelonin | BLyS-gelonin | B lymphocyte stimulator (BLyS) | BR3/BAFF-R, TACI and BCMA | B-NHL subtypes mantle cell lym-phoma (MCL), dif-fuse large B-cell lymphoma (DLBCL), B-cell precursor-acute lymphocytic leukemia (BCP-ALL) | Yes | Yes | | [348-350] |
| Gelonin | C6.5-rGel | scFv (C6.5) | HER2 | Breast cancer, gastric cancer, lung cancer, ovarian cancer | Yes | Yes | | [351] |
| Gelonin | e23-L-rGel | scFv (e23) | HER2 | Breast cancer, gastric cancer, lung cancer, ovarian cancer | Yes | | | [352] |
| Gelonin | ML3-9-rGel | scFv (ML3-9) | HER2 | Breast cancer, gastric cancer, lung cancer | Yes | Yes | | [351] |
| Gelonin | MH3-B1-rGel | scFv (MH3-B1) | HER2 | Breast cancer, gastric cancer, lung cancer | Yes | Yes | | [351] |
| Gelonin | B1D3-rGel | scFv (B1D3) | HER2 | Breast cancer, gastric cancer, lung cancer | Yes | Yes | | [351] |
| Gelonin | 3ErGel | scFv (sm3E) | Carcinoembryonic antigen (CEA) | Colorectal cancer | Yes | | | [353] |
| Gelonin | FErGel | scFv (shMFE) | Carcinoembryonic antigen (CEA) | Colorectal cancer | Yes | | | [353] |
| Gelonin | C7rGel | FN3 fragment (C743) | Carcinoembryonic antigen (CEA) | Colorectal cancer | Yes | Yes | | [353, 354] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Gelonin | E4rGel | FN3 fragment (E246) | EGFR | Colorectal cancer | Yes | Yes | | [353, 354] |
| Gelonin | 3C/rGel | scFv (3C) | FGFR3 | Multiple myeloma, hepatocellular carcinoma, bladder cancer | Yes | Yes | | [355, 356] |
| Gelonin | 7D/rGel | scFv (7D) | FGFR3 | Multiple myeloma, hepatocellular carcinoma, bladder cancer | Yes | Yes | | [355] |
| Gelonin | H45-rGelonin$_{D274C}$ | mAb (H45) | CD5 | ALL | Yes | Yes | | [357] |
| Gelonin | MOC31-gelonin | mAb (MOC31) | Epithelial glycoprotein-2 (EGP-2) | SCLC, colon cancer, breast cancer | Yes | | | [358] |
| Luffa ribosomal inhibitory protein (LRIP) | HB21-LRIP | mAb (HB21) (5E9) | TfR | T lymphoblastic leukemia | Yes | | | [168] |
| Luffin-A | Luffin A-Ng76 | mAb (Ng76) | Melanoma antigen | Melanoma | Yes | | | [359] |
| Luffin-B | Luffin B-Ng76 | mAb (Ng76) | Melanoma antigen | Melanoma | Yes | | | [360] |
| Luffin-B | LKP (Luffin-β-KDEL-uPAcs) | uPAcs (urokinase-type plasminogen activator) | Urokinase receptor | Non-small cell lung cancer (NSCLC) | Yes | | | [361] |
| Luffin-P1 | hIL-2-Luffin P1 | IL-2 | CD25 (IL-2 receptor) | Activated lymphocytes | Yes | Yes | | [362-364] |
| Luffin-P1 | EBI3-Luffin P1 | EBI3 (Epstein-Barr virus (EBV)-induced gene 3) | CD25 (IL-2 receptor) | Immunological diseases, erythroleukemia | Yes | | | [365] |
| Mistletoe lectin I A-chain | Anti-CD5/MLIA | mAb (anti-CD5) | CD5 | T-lymphocytes | Yes | | | [366] |
| Mistletoe lectin I A-chain | Anti-CD25/MLIA (Anti-CD25-MLA) | mAb (anti-CD25) | CD25 (IL-2 receptor) | Activated lymphocytes | Yes | | | [367] |
| Mistletoe lectin I A-chain | MoAb-16-MLIA | mAb (16) | Oncofetal antigen | Leukemia | Yes | | | [368] |
| Mistletoe lectin I A-chain | BMAC1/MLA | mAb (BMCA1) | CD45 | Allograft rejection | Yes | | | [369] |
| Mistletoe lectin I A-chain | OX1/MLA | mAb (OX1) | rat CD45 | Allograft rejection | Yes | | | [369] |
| Momorcochin | Anti-epithelial antigen-momorcochin | mAb (anti-epithelial antigen) | Epithelial antigen | Colon cancer, epidermoid carcinoma | Yes | | | [302] |
| Momorcochin | F(ab')$_2$-momorcochin/UCHT1 | F(ab')$_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Momorcochin-S | Momorcochin-S-A8 | mAb (8A) | 8A myeloma antigen | Burkitt lymphoma | Yes | Yes | | [193] |
| Momordin | OX7-momordin | mAb (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | AKR-A lymphoma | Yes | | | [298] |
| Momordin | Fib 75-momordin | mAb (LICR-LOND Fib 75) | Bladder cancer antigen | EJ bladder cancer | Yes | Yes | | [284, 312] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Momordin | OM124-momordin | mAb (anti-CD22) (OM124) | CD22 | Burkitt's B-cell lymphoma, Epstein-Barr virus-infected B lymphoblastoid cells | Yes | Yes | | [370] |
| Momordin | 8A-Momordin | mAb (8A) | 8A myeloma antigen | Multiple myeloma | Yes | | | [371] |
| Momordin | Anti-CD5-Momordin | mAb (anti-CD5) | CD5 | T-cell leukemia | Yes | Yes | | [372] |
| Momordin | Anti-CD30-Momordin (Ber-H2-Momordin) | mAb (Ber-H2) | CD30 | Hodgkin's lymphoma, anaplastic large-cell lymphoma(ALCL) | Yes | Yes | | [307, 373, 374] |
| Momordin | BDI-1-momordin | mAb (BDI-1) | Bladder cancer antigen | Bladder cancer | Yes | Yes | Phase I | [375, 376] |
| Momordin | Folate-momordin | Folate | Folate receptor | Cervical cancer, ovarian cancer | Yes | | | [377, 378] |
| Momordin | Anti-epithelial antigen-momordin | mAb (anti-epithelial antigen) | Epithelial antigen | Colon cancer, epidermoid carcinoma | Yes | | | [302] |
| Momordin | $F(ab')_2$-momordin/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Momordin I | 48-127/momordin I | mAb (48-127) | gp54 | Bladder cancer | Yes | | | [379] |
| Moschatin | Moschatin-Ng76 | mAb (Ng76) | Melanoma antigen | Melanoma | Yes | | | [380] |
| Nigrin b | 44G4-nigrin b | mAb (44G4) | CD105 (endoglin) | Tumor neovasculature | Yes | | | [381] |
| Nigrin b | MJ7-Ngb | mAb (MJ7/18) | CD105 (endoglin) | Tumor neovasculature, melanoma | Yes | Yes | | [382, 383] |
| Nigrin b | Nigrin b-transferrin | Transferrin | TfR | TfR-over-expressing cancer cells | Yes | | | [310] |
| Ocymoidine | Mint-Ocy | mAb (Mint5) | EGFR | Breast cancer | Yes | Yes | | [384] |
| PAP | B43-PAP | mAb (B43) | CD19 | Leukemia, B-cell ALL | Yes | Yes | Phase I | [385-388] |
| PAP | TXU-PAP | mAb (TXU) | CD7 | T-NHL, HIV type I | Yes | Yes | Phase I | [389-391] |
| PAP | Anti-Thy 1.1 (mAb)-PAP | mAb (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | Leukemia | Yes | | | [392] |
| PAP | Anti-Thy 1.1 ($F(ab')_2$)-PAP | $F(ab')_2$ (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | Leukemia | Yes | | | [392] |
| PAP | GnRH-PAP | Gonadotropinreleasing hormone (GnRH) | GnRH receptor | Breast cancer | Yes | | | [393, 394] |
| PAP | TP3-PAP | mAb (TP3) | p80 | Osteosarcoma | Yes | Yes | | [395] |
| PAP | J3-109-PAP | mAb (J3-109) | CD72 | B-cell ALL | Yes | | | [396] |
| PAP | 74-12-4-PAP | mAb (74-12-4) | porcine CD4 | Transplants | | Yes | | [397] |
| PAP | Anti-CD4-PAP | mAb (MT151) | CD4 | HIV | Yes | | | [398] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| PAP | PAP-9.2.27 | mAb (9.2.27) | Melanoma-associated antigen (p250) | Melanoma | Yes | Yes | | [280, 399] |
| PAP | J5/PAP | mAb (J5) | CD10 (CALLA) | Lymphoma | Yes | | | [314] |
| PAP9 (High expressed mutated PAP) | PAP9-IL-2 | IL-2 | CD25 (IL-2 receptor) | T-cell lymphoma | Yes | | | [400] |
| PAP II | J5/PAP II | mAb (J5) | CD10 (CALLA) | Lymphoma | Yes | | | [314] |
| PAP-S | OM124-PAP-S | mAb (anti-CD22) (OM124) | CD22 | Burkitt's B-cell lymphoma, Epstein-Barr virus-infected B lymphoblastoid cells, Hodgkin's lymphoma | Yes | Yes | | [307, 370] |
| PAP-S | Anti-CD30-PAP-S (Ber-H2-PAP-S) | mAb (Ber-H2) | CD30 | Hodgkin's lymphoma, anaplastic large-cell lymphoma(ALCL) | Yes | Yes | | [373, 401] |
| PAP-S | 48-127/PAP-S | mAb (48-127) | gp54 | Bladder cancer | Yes | | | [379] |
| PAP-S | Anti-epithelial antigen-PAP-S | mAb (anti-epithelial antigen) | Epithelial antigen | Colon cancer, epidermoid carcinoma | Yes | | | [302] |
| PAP-S | $F(ab')_2$-PAP-S/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| PAP-S | J5/PAP-S | mAb (J5) | CD10 (CALLA) | Lymphoma | Yes | | | [314] |
| PD-S2 | Ber-H2-PD-S2 | mAb (Ber-H2) | CD30 | Hodgkin's lymphoma | Yes | | | [307] |
| Pyramidatine | Mint-Pyra | mAb (Mint5) | EGFR | Breast cancer | Yes | Yes | | [384] |
| Ricin | Anti-Ly2.1-ricin | mAb (anti-Ly2.1) | Murine T-cell antigen | T-cell ALL | Yes | Yes | | [402] |
| Ricin | Anti-CD8-ricin | mAb (B9.4.2) | CD8 | PBMCs | Yes | | | [403] |
| Ricin | Anti-CD4-ricin | mAb (HP2/6) | CD4 | PBMCs | Yes | | | [403] |
| Ricin | Anti-CD3-ricin | mAb (SPV-T3b) | CD3 | PBMCs | Yes | | | [403] |
| Ricin | Anti-CD3-ricin | mAb (11D8) | CD3 | PBMCs | Yes | | | [403] |
| Ricin | UCHT1-ricin | mAb (UCHT1) | CD3ε | GVHD | Yes | | | [404] |
| Ricin | 35.1-ricin | mAb (35.1) | CD2 | GVHD | Yes | | | [404] |
| Ricin | T101-ricin | mAb (T101) | CD5 | GVHD | Yes | Yes | | [404, 405] |
| Ricin | Ricin-HB55 | mAb (BH55) | HLA-DR | B-cell leukemia, lymphoma | Yes | | | [406] |
| Ricin | IL2-lectin-deficient RTB-RTA | IL-2 | CD25 (IL-2 receptor) | Leukemia | Yes | | | [407] |
| Ricin | GMCSF-ricin | GMCSF | GMCSF receptor | AML | Yes | | | [408] |
| Ricin | M6-ricin | mAb (M6) | $L_2C$ IgM idiotype | B-cell leukemia | Yes | Yes | | [409] |
| Ricin | Anti-GE2-ricin | mAb (anti-GE2) | GE2 | Glioma | Yes | | | [410] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Ricin | AR3-ricin | mAb (AR3) | CAR-3 | Gastric cancer, colo-rectal cancer | Yes | | | [411] |
| Ricin | BDI-1-ricin | mAb (BDI-1) | Bladder cancer anti-gen | Bladder cancer | Yes | | | [412] |
| Ricin | Ricin-mAb 35 | mAb (35) | AChR (nicotinic acetylcholine recep-tor) | Strabismus | Yes | Yes | | [413, 414] |
| Ricin | Anti-Lyt 2.2-ricin | mAb (anti-Lyt 2.2) (19/178$C_1$) | Lyt2.2 | T-cell lymphoma | Yes | | | [331] |
| Ricin | IgE-intact ricin | mAb (IR162) | IgE Fc receptor | Allergies, basophil leukemia | Yes | | | [415] |
| Ricin | L6-ricin | mAb (L6) | Lung canger antigen | Lung cancer | Yes | Yes | | [416] |
| Ricin | Ricin-EGF | EGF | EGFR | Epidermoid carci-noma | Yes | | | [417] |
| Ricin | Anti-CD6-bR | mAb (anti-CD6) | CD6 | CTCL, ALL | Yes | Yes | Phase I | [418, 419] |
| Ricin | Anti-B4-bR | mAb (anti-B4) | CD19 | B-NHL | Yes | Yes | Phase III | [420-425] |
| Ricin | Anti-My9-bR | mAb (anti-My9) | CD33 | AML | Yes | Yes | Phase I | [418, 426, 427] |
| Ricin | N901-bR | mAb (N901) | CD56 (N-CAM) | SCLC | Yes | Yes | Phase II | [418, 428-431] |
| Ricin | Anti-CEA-bR | mAb (I-1) | Carcinoembryonic antigen (CEA) | Colorectal cancer | Yes | Yes | Phase I/II | [432] |
| Ricin | IF7-bR | mAb (IF7) | CD26 | T cells | Yes | | | [433] |
| Ricin | 4B4-bR | mAb (4B4) | CD29 | Lymphocytes, endo-thelium | Yes | | | [304] |
| Ricin | MT151-blocked ricin | mAb (MT151) | CD4 | ALL | Yes | | | [434] |
| Ricin | Anti-CD4.CD26-bRicin | Bispecific mAb (anti-CD4 x CD26) | CD4 + CD26 | GVHD | Yes | | | [433] |
| Ricin | Anti-CD4-bRicin | Fab' (19thy5D7) | CD4 | GVHD | Yes | | | [433] |
| Ricin | Anti-CD26-bRicin | Fab' (1F7) | CD26 | GVHD | Yes | | | [433] |
| Ricin | Anti-CD4.CD29-bRicin | Bispecific mAb (anti-CD4 x CD29) | CD4 + CD29 | Tissue allografts | Yes | | | [435] |
| Ricin | SEN31-bR | mAb (SEN31) | Cluster-5a antigen | SCLC | Yes | Yes | | [436] |
| Ricin | HB7-blocked ricin | mAb (HB7) | CD38 | Multiple myeloma, lymphoma | Yes | | | [437] |
| RTA | Anti-Thy 1.1-dgRTA | mAb (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | AKR-A lymphoma | Yes | Yes | | [438] |
| RTA | Anti-CD7-dgA (DA7) | mAb (3A1e) | CD7 | T-NHL, leukemia, GVHD | Yes | Yes | Phase I | [439] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | HD37-dgA (IMTOX-19) | mAb (HD37) | CD19 | B-NHL, ALL | Yes | Yes | Phase I | [440, 441] |
| RTA | RFB4-Fab'-dgA | Fab' (RFB4) | CD22 | B-NHL, leukemia, lymphoma | Yes | Yes | Phase I | [442, 443] |
| RTA | RFT5-dgA (IMTOX-25) | mAb (RFT5) | CD25 | Hodgkin's lymphoma, CTCL, melanoma, GVHD | Yes | Yes | Phase II | [444-448] |
| RTA | Ki-4.dgA | mAb ($K_i$-4) | CD30 | Hodgkin's lymphoma, NHL | Yes | Yes | Phase I | [447, 449, 450] |
| RTA | RFB4-dgA (IMTOX-22) | mAb (RFB4) | CD22 | B-NHL, CLL, ALL, leukemia, lymphoma, myeloma | Yes | Yes | Phase I | [443, 451, 452] |
| RTA | Combotox (RFB4-dgA / HD37-dgA) | mAb (RFB4) + mAb (HD37) | CD22, CD19 | NHL, ALL | Yes | Yes | Phase I | [453, 454] |
| RTA | SPV-T3a-dgA + WT1-dgA | mAb (SPV-T3a) + mAb (WT1) | CD3, CD7 | GVHD | Yes | Yes | Phase I/II | [455, 456] |
| RTA | 3A1e-dgRTA | scFv (3A1e) | CD7 | T-cell leukemia | Yes | | | [457] |
| RTA | 3AIf-dgRTA | scFv (3A1f) | CD7 | T-cell leukemia | Yes | | | [457] |
| RTA | UV3-dgRTA | mAb (UV3) | CD54 (ICAM-1) | Myeloma, grnulocytes, monocytes | Yes | | | [458] |
| RTA | H22-dgRTA (CD64-RiA) | mAb (H22) | CD64 | AML, rheumatoid arthritis, monocytes, macrophages | Yes | Yes | | [459-461] |
| RTA | D5-dgA | mAb (D5) | Cytomegalovirus | Cytomegalovirus (MCMV) | Yes | | | [462] |
| RTA | C34-dgA | mAb (C34) | Cytomegalovirus | Cytomegalovirus (MCMV) | Yes | | | [462] |
| RTA | HMS-dgA | IgG (HMS) | Cytomegalovirus | Cytomegalovirus (MCMV) | Yes | | | [462] |
| RTA | 64.1-dgRTA | mAb (64.1) | CD3 | Lymphoproliferative disease (LPD) | Yes | Yes | | [463, 464] |
| RTA | HD6-dgA | mAb (HD6) | CD22 | Leukemia, lymphoma | Yes | | | [443] |
| RTA | HD6-Fab'-dgA | Fab' (HD6) | CD22 | Leukemia, lymphoma | Yes | | | [443] |
| RTA | UV22-1-dgA | mAb (UV22-1) | CD22 | Leukemia, lymphoma | Yes | | | [443] |
| RTA | UV22-1-Fab'-dgA | Fab' (UV22-1) | CD22 | Leukemia, lymphoma | Yes | | | [443] |
| RTA | UV22-2-dgA | mAb (UV22-2) | CD22 | Leukemia, lymphoma | Yes | | | [443] |
| RTA | UV22-2-Fab'-dgA | Fab' (UV22-2) | CD22 | Leukemia, lymphoma | Yes | | | [443] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | p67.7-dgA | mAb (p67.7) | CD33 | AML | Yes | | | [465] |
| RTA | 120-2A3-dgA | mAb (120-2A3) | TfR | Myeloma, Hodgkin's lymphoma | Yes | | | [465] |
| RTA | B-B10-dgA | mAb (B-B10) | CD25 (IL-2 receptor) | Myeloma, Hodgkin's lymphoma | Yes | | | [465] |
| RTA | TDR31-1-dgA | mAb (TDR31-1) | MHC class II | Myeloma, Hodgkin's lymphoma | Yes | | | [465] |
| RTA | SWA11-dg.RTA | mAb (SWA11) | CD24 | SCLC | Yes | Yes | | [466, 467] |
| RTA | M5/114-dgA | mAb (M5/114) | MCH Class II antigens ($I\text{-}A^d$, $I\text{-}E^d$) | Endothelial cells | Yes | Yes | | [468] |
| RTA | 11-4.1-dgA | mAb (11-4.1) | MCH Class I antigen ($H\text{-}2K^k$) | Neuroblastoma | Yes | Yes | | [468, 469] |
| RTA | E6-dgA | mAb (E6) | Prostate-specific membrane antigen (PSMA) | Prostate cancer | Yes | Yes | | [470] |
| RTA | 14G2a.dgA | mAb (14G2a) | Disialoganglioside GD2 | Neuroblastoma | Yes | Yes | | [471] |
| RTA | ch14.18.dgA | mAb (ch14.18) | Disialoganglioside | Neuroblastoma | Yes | | | [471] |
| RTA | BW704.dgA | mAb (BW704) | Disialoganglioside | Neuroblastoma | Yes | | | [471] |
| RTA | chCE7.dgA | mAb (chCE7) | 190 kDa Glycoprotein (gp190) | Neuroblastoma | Yes | | | [471] |
| RTA | FVS191cys-dgRTA | scFv (FVS191) | CD19 | Leukemia | Yes | | | [472] |
| RTA | K4-2C10-dgRA | mAb (K4-2C10) | CD105 (endoglin) | Tumor neovasculature, breast cancer | Yes | Yes | | [473] |
| RTA | SN6j-dgRA | mAb (SN6j) | CD105 (endoglin) | Tumor neovasculature, breast cancer | Yes | Yes | | [474] |
| RTA | SN6k-dgRA | mAb (SN6k) | CD105 (endoglin) | Tumor neovasculature, breast cancer | Yes | Yes | | [474] |
| RTA | D5-dgA | mAb (D5) | MCMV antigen (murine cytomegalovirus antigen) | CMV infection | Yes | Yes | | [462, 475] |
| RTA | C34-dgA | mAb (C34) | MCMV antigen (murine cytomegalovirus antigen) | CMV infection | Yes | Yes | | [462, 475] |
| RTA | FF1-4D5-dgA | mAb (FF1-4D5) | mouse δ H chain of surface IgD (mδsIgD), domain Fd | B-cells | Yes | | | [476] |
| RTA | AMS-15.1-dgA | mAb (AMS-15.1) | mouse δ H chain of surface IgD (mδsIgD), domain Fd | B-cells | Yes | | | [476] |
| RTA | 11-26-dgA | mAb (11-26) | mouse δ H chain of surface IgD (mδsIgD), domain Fd | B-cells | Yes | | | [476] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | JA12.5-dgA | mAb (JA12.5) | mouse δ H chain of surface IgD (mδsIgD), domain Fd | B-cells | Yes | | | [476] |
| RTA | AMS-9.1-dgA | mAb (AMS-9.1) | mouse δ H chain of surface IgD (mδsIgD), domain Fc | B-cells | Yes | | | [476] |
| RTA | AMS-28.1-dgA | mAb (AMS-28.1) | mouse δ H chain of surface IgD (mδsIgD), domain Fc | B-cells | Yes | | | [476] |
| RTA | $H\delta^a/1$-dgA | mAb ($H\delta^a/1$) | mouse δ H chain of surface IgD (mδsIgD), domain Fc | B-cells | Yes | | | [476] |
| RTA | UCHL1-dgA | mAb (UCHL1) | CD45RO | HIV | Yes | | | [477-479] |
| RTA | My7/Fab' GAMIg.dgA | mAb (My7) / Fab' (GAM Ig) | CD13 | Myeloid leukemia | Yes | | | [465] |
| RTA | 1G10/Fab' GAMIg.dgA | mAb (My7) / Fab' (GAM Ig) | CD15 | Myeloid leukemia | Yes | | | [465] |
| RTA | rCD4-dgA | rCD4 (recombinant CD4) | HIVgp120 | HIV | Yes | | | [480] |
| RTA | Fib 75-ricin A chain | mAb (LICR-LOND Fib 75) | Bladder cancer antigen | Bladder cancer | Yes | Yes | | [282-284] |
| RTA | ITR | IgG (anti-Trypanosoma cruzi surface antigens) | Trypanosoma cruzi surface antigens | *Trypanosoma cruz*i | Yes | | | [288] |
| RTA | Anti-CD25/RTA | mAb (anti-CD25) | CD25 (IL-2 receptor) | Activated lymphocytes | Yes | | | [367, 407] |
| RTA | Anti-CD5/RTA | mAb (anti-CD5) | CD5 | T-lymphocytes | Yes | | | [366] |
| RTA | BerH2-RTA | mAb (Ber-H2) | CD30 | Lymphoblastoid, Hodgkin's lymphoma | Yes | | | [374, 481] |
| RTA | H65-RTA (CD5 Plus) (XomaZyme-CD5 Plus) | mAb (H65) | CD5 | GVHD, CTCL, CLL, rheumatoid arthritis, systemic lupus erythematosus (SLE), diabetes mellitus | Yes | Yes | Phase II | [482-487] |
| RTA | 454A12-rRA | mAb (454A12) | TfR | Breast cancer, leptomeningeal neoplasia | Yes | Yes | Phase I | [488, 489] |
| RTA | 260F9-rRTA | mAb (260F9) | 55 kDa breast cancer antigen (p55) | Breast cancer, ovarian cancer | Yes | Yes | Phase I | [490-492] |
| RTA | XMMME-001-RTA (XomaZyme-Mel) | mAb (XMMME-001) | Melanoma antigen (Proteoglycan) | Melanoma | Yes | Yes | Phase I/II | [493-498] |
| RTA | 791T/36-RTA (XomaZyme-791) | mAb (791T/36) | 72 kDa cancer antigen (72 kDa TAA) (p72) | Colorectal cancer | Yes | Yes | Phase I | [499, 500] |
| RTA | T101-RTA | mAb (T101) | CD5 | CLL | Yes | Yes | Phase I | [501-503] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | T101-RTA | Fab (T101) | CD5 | T-cell leukemia | Yes | | | [504] |
| RTA | T101-RTA | $F(ab')_2$ (T101) | CD5 | T-cell leukemia | Yes | | | [504] |
| RTA | MDX-RA (4197X-RA) | mAb (4197X) | Human lens epithelial antigen | Posterior capsule opacification (secondary cataract) | | Yes | Phase III | [505-507] |
| RTA | RTA-EGF | EGF | EGFR | Epidermoid carcinoma, EGFR+ cells | Yes | | | [84, 417, 508] |
| RTA | WT82-RTA | mAb (WT82) | CD8 | T-cell ALL | Yes | | | [509] |
| RTA | 2G5-RTA | mAb (2G5) | HLA-DR | Lymphoma, B cells, T cells, dendritic cells | Yes | | | [510] |
| RTA | CLL2m-RTA | mAb (CLL2m) | CLL2m antigen | ND, CLL | Yes | | | [511] |
| RTA | HAE3-RTA | mAb (HAE3) | Glycophorin-A | Erythromyeloblastoid leukemia | Yes | | | [512] |
| RTA | HAE9-RTA | mAb (HAE9) | Erythroid antigen | Erythromyeloblastoid leukemia | Yes | | | [512] |
| RTA | BMAC1/RTA | mAb (BMCA1) | CD45 | Allograft rejection | Yes | | | [369] |
| RTA | OX1/RTA | mAb (OX1) | rat CD45 | Allograft rejection | Yes | | | [369] |
| RTA | SN7-RTA | mAb (SN7) | SN7 B-cell antigen | B-cell leukemia, B-cell lymphoma | Yes | Yes | | [513] |
| RTA | HB21-RTA | mAb (HB21) (5E9) | TfR | Ovarian cancer, epidermoid carcinoma | Yes | | | [492] |
| RTA | R17217-rRTA | mAb (R17217) | Murine TfR | Lymphoma | Yes | Yes | | [514] |
| RTA | YE1/9.9-rRTA | mAb (YE1/9.9) | Murine TfR | Lymphoma | Yes | | | [514] |
| RTA | 0.5beta-RTA | mAb (0.5beta) | HIV gp120 | HIV | Yes | | | [515] |
| RTA | Anti-gp120-RTA | mAb (anti-gp120) | HIV gp120 | HIV | Yes | | | [516] |
| RTA | Anti-gp120-RTA | IgG (anti-gp120) | HIV gp120 | HIV | Yes | | | [517] |
| RTA | Anti-gp41-RTA | mAb (7B2) | HIV gp120 | HIV | Yes | Yes | | [516, 518, 519] |
| RTA | 171A-RTA | mAb (171A) | EpCAM | Colorectal cancer | Yes | | | [520] |
| RTA | MT151-RTA | mAb (MT151) | CD4 | ALL | Yes | | | [434] |
| RTA | MRK-RTA | mAb (MRK16) | P-glycoprotein | Kidney cancer | Yes | | | [521] |
| RTA | KM231-RTA | mAb (KM231) | Sialyl-Lea-antigen | Gastric cancer, colorectal cancer | Yes | Yes | | [522] |
| RTA | UCHT1 $F(ab')_2$-RTA | $F(ab')_2$ (UCHT1) | CD3ε | GVHD | Yes | Yes | | [523] |
| RTA | WT32-RTA | mAb (WT32) | CD3 | T-cell ALL | Yes | | | [524] |
| RTA | WT1-RTA | mAb (WT1) | CD7 | T-cell ALL, lymphoma | Yes | | | [524, 525] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | 528-rRA | mAb (528) | EGFR | Lung cancer | Yes | Yes | | [526] |
| RTA | Anti-Tac-RTA | mAb (anti-CD25) | CD25 (IL-2 receptor) | T-cell leukemia, activated lympho-cytes | Yes | | | [367, 527] |
| RTA | Tf-RTA | Transferrin | TfR | T-cell ALL, prostate cancer, malaria (*Plasmodium falci-parum*) | Yes | | | [327, 528, 529] |
| RTA | Tf-KFT25-RTA | Transferrin | TfR | T-cell ALL | Yes | | | [528] |
| RTA | 520C9-RTA | mAb (520C9) | HER2 | Breast cancer | Yes | | | [530] |
| RTA | 741 F8-RTA | mAb (741 F8) | HER2 | Breast cancer | Yes | | | [530] |
| RTA | 454C11-RTA | mAb (454C11) | HER2 | Breast cancer | Yes | | | [530] |
| RTA | STI-RTA | mAb (STI) | CD5 | T-cell ALL | Yes | | | [531] |
| RTA | RTA-9.2.27 | mAb (9.2.27) | Melanoma-associated antigen (p250) | Melanoma | Yes | Yes | | [280] |
| RTA | BrE-3-RTA | mAb (BrE-3) | Mucin, MUC1 | SCLC | Yes | | | [532] |
| RTA | C242-RTA (ICI D0490) | mAb (C242) | Mucin | Colorectal cancer | Yes | Yes | | [533] |
| RTA | 84.1c-RTA | mAb (84.1c) | mIgE | Allergies | Yes | Yes | | [534] |
| RTA | HRS-3.dgA | mAb (HRS-3) | CD30 | Hodgkin's lym-phoma, myeloma | Yes | | | [465, 535] |
| RTA | HRS-3Fab'.dgA | Fab' (HRS-3) | CD30 | Hodgkin's lymphoma | Yes | | | [535] |
| RTA | HRS-4.dgA | mAb (HRS-4) | CD30 | Hodgkin's lymphoma | Yes | | | [535] |
| RTA | HRS-4Fab'.dgA | Fab' (HRS-4) | CD30 | Hodgkin's lymphoma | Yes | | | [535] |
| RTA | HRS-1.dgA | mAb (HRS-1) | CD30 | Hodgkin's lymphoma | Yes | | | [535] |
| RTA | $^{90}$Y-C110-RTA | mAb (C110) | Carcinoembryonic antigen (CEA) | Colon cancer | Yes | Yes | | [536] |
| RTA | C19-RTA | mAb (C19) | Carcinoembryonic antigen (CEA) | Colorectal cancer | Yes | | | [537] |
| RTA | M6-RTA | mAb (M6) | $L_2C$ IgM idiotype | B-cell leukemia | Yes | Yes | | [409] |
| RTA | 38.13-RTA | mAb (38.13) | TH ceramide (Pk antigen) | Burkitt's lymphoma | Yes | | | [324] |
| RTA | Fab'-anti-L3T4-A | Fab' (anti-L3T4) | Murine T-cell anti-gen (limpet hemo-cyanin-specific T-helper lymphocytes) | Lymphoma | Yes | | | [538] |
| RTA | 486P-RTA | mAb (486P 3-12-1) | Bladder cancer anti-gen | Bladder cancer | Yes | | | [539] |
| RTA | RFT11-A | mAb (RFT11) | CD2 | T-cell ALL | Yes | | | [540] |
| RTA | 35.1-A | mAb (35.1) | CD2 | T-cell ALL | Yes | | | [464, 540] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | 9.6-A | mAb (9.6) | CD2 | T-cell ALL | Yes | | | [464, 540] |
| RTA | 10.2-A | mAb (10.2) | CD5 | T cells | Yes | | | [464] |
| RTA | 452-D9-RTA | mAb (452-D9) | gp74 | c-Ha-ras expression tumors, Kirsten sarcoma | Yes | Yes | | [541, 542] |
| RTA | Thyroglobulin-RTA | Thyroglobulin | Ig (anti-thyroglobulin) | Thyroiditis | Yes | | | [543] |
| RTA | 96.5-RTA | mAb (96.5) | p97 | Melanoma | Yes | | | [544] |
| RTA | SN5d-RTA | mAb (SN5d) | CD10 (CALLA) | Pre-B-cell ALL | Yes | Yes | | [545] |
| RTA | SN5-RTA | mAb (SN5) | CD10 (CALLA) | Pre-B-cell ALL | Yes | Yes | | [545] |
| RTA | Anti-CALLA-RTA | mAb (anti-CALLA) | CD10 (CALLA) | Burkitt's lymphoma, (pre-B-cell ALL) | Yes | | | [546] |
| RTA | Anti-CALLA-RTA | Fab' (anti-CALLA) | CD10 (CALLA) | Burkitt's lymphoma, (pre-B-cell ALL) | Yes | | | [546] |
| RTA | Anti-GE2-RTA | mAb (anti-GE2) | GE2 | Glioma | Yes | | | [410] |
| RTA | D1/12-RTA | mAb (D1/12) | HLA-DR | Glioma | Yes | | | [410] |
| RTA | AR3-RTA | mAb (AR3) | CAR-3 | Gastric cancer | Yes | | | [411] |
| RTA | 8C-RTA | mAb (8C) | Ovarian cancer antigen | Ovarian cancer | Yes | Yes | | [547] |
| RTA | M2A-RTA | mAb (M2A) | Ovarian cancer antigen | Ovarian cancer | Yes | Yes | | [547] |
| RTA | Anti-vasopressin-RTA | mAb (anti-vasopressin) | Vasopressin | Pituitary cancer | Yes | Yes | | [548] |
| RTA | Cluster 2 Mab-Fab'-Anti-Mouse/RAT-RTA | mAb (Cluster 2) | Cluster 2 antigen-SCLC | SCLC | Yes | | | [549] |
| RTA | SOKT1-RTA | mAb (SOKT1) | T-cell antigen | T cells | Yes | | | [550] |
| RTA | MGb2-RTA | mAb (MGb2) | Gastric antigen | Gastric cancer | Yes | | | [551] |
| RTA | MG11-RTA | mAb (MG11) | Gastric antigen | Gastric cancer | Yes | | | [551] |
| RTA | MoAb-16-RTA | mAb (16) | Oncofetal antigen | Leukemia | Yes | Yes | | [368, 552] |
| RTA | Anti-laryngeal cancer-RTA | mAb (anti-laryngeal cancer) | Laryngeal cancer antigen | Laryngeal cancer | Yes | | | [553, 554] |
| RTA | 317G5-RTA | mAb (317G5) | 42 kDa glycoprotein (p42) | Breast cancer | Yes | | | [555] |
| RTA | SEN36-RTA | mAb (SEN36) | CD56 (N-CAM) | SCLC | Yes | | | [556] |
| RTA | Anti-mu-RTA | mAb (anti-mu) | Mu chain of IgM | Myeloma | Yes | | | [557] |
| RTA | SEN7-bR | mAb (SEN7) | CD56 (N-CAM) | SCLC | Yes | | | [558] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| RTA | Anti-CRF-RTA | mAb (anti-CRF) | CRF (corticotropin-releasing factor) | Immunolesioning (CRF neurons within the paraventricular nucleus of the hypothalamus) | | Yes | | [559] |
| RTA | Anti-asialo-GM2-RTA | mAb (anti-asialo-GM2) | Asialo-GM2 | Lymphoma | Yes | | | [560] |
| RTA | Anti-H-2d-RTA | mAb (anti-H-2d) | H-2d | Lymphoma | Yes | | | [560] |
| RTA | V beta 6-specific immunotoxin (VIT6) | mAb (anti-V beta 6-specific) | V beta-associated antigen receptor | Myasthenia gravis | Yes | | | [561] |
| RTA | schM21-ricin A | scFv (schM21) | Astrocytoma- and medulloblastoma-associated antigen | Medulloblastoma | Yes | | | [562] |
| RTA | ONS-M21-RTA (ORA) | mAb (ONS-M21) | Astrocytoma- and medulloblastoma-associated antigen | Medulloblastoma | Yes | | | [563] |
| RTA | Anti-VIP-RTA | mAb (anti-VIP) | Vasoactive intestinal polypeptide (VIP) | Pheochromocytoma, immunolesioning (neurons within the SCN) (suprachiasmatic nucleus of the hypothalamus) | Yes | Yes | | [564] |
| RTA | Anti-Thy 1.2-RTA | IgG (anti-Thy 1.2) | CD90.2 (Thy 1.2) | Leukemia | Yes | Yes | | [565] |
| RTA | IgE-ricin A-chain | mAb (IR162) | IgE Fc receptor | Allergies, basophil leukemia | Yes | Yes | | [566, 567] |
| RTA | OX-40-ricin A | mAb (anti-OX-40) | OX-40 | Autoimmune encephalomyelitis (EAE) | Yes | Yes | | [568] |
| RTA | SWA20-RTA | mAb (SWA20) | CD24 | SCLC | Yes | | | [467] |
| RTA | Anti-T. cruzi-RTA | IgG (anti-Trypanosoma cruzi surface antigens) | Trypanosoma cruzi surface antigens | *Trypanosoma cruzi* | Yes | Yes | | [288] |
| RTA | UCHT1/F(ab')$_2$-ricin A chain | mAb (UCHT1) / F(ab')$_2$ (anti-IgG) | CD3 | T-cell lymphoma | Yes | | | [303] |
| RTA | RTA-NIM-R7 | mAb (NIM-R7) | p58 | Lymphoma | Yes | | | [569] |
| Saporin | Anti-Thy 1.1 (F(ab')$_2$)-saporin | F(ab')$_2$ (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | AKR-A lymphoma | Yes | Yes | | [570] |
| Saporin | Anti-Thy 1.1 (mAb)-saporin | mAb (anti-Thy 1.1) (OX7) | CD90.1 (Thy 1.1) | AKR-A lymphoma | Yes | Yes | | [570] |
| Saporin | 192 IgG-saporin (192-IgG-SAP) (IgG-192) | mAb (192) | Rat nerve growth factor receptor (p75NTR) | Immunolesioning (cholinergic basal forebrain neurons), Alzheimer's disease | Yes | Yes | | [571-574] |
| Saporin | OM124-saporin | mAb (OM124) | CD22 | Burkitt's B-cell lymphoma, Epstein-Barr virus-infected B lymphoblastoid cells | Yes | Yes | | [370] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | M24-saporin (anti-CD80/saporin) | mAb (M24) | CD80 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | | | [295] |
| Saporin | 1G10-saporin (anti-CD86/saporin) | mAb (1G10) | CD86 | Hodgkin's lymphoma, Burkitt's lymphoma | Yes | | | [295] |
| Saporin | M24-saporin / 1G10-saporin | mAb (M24) / mAb (1G10) | CD80 + CD86 | Burkitt's lymphoma, Hodgkin's lymphoma | Yes | | | [295] |
| Saporin | OKT11-saporin | mAb (OKT11) | CD2 | T-CLL | Yes | | | [575, 576] |
| Saporin | 7A10C9-saporin | mAb (7A10C9) | CD2 | T-CLL | Yes | | | [575] |
| Saporin | OKT1-saporin | OKT1 | CD5 | T-lymphocytes, B-CLL | Yes | Yes | | [577-579] |
| Saporin | BsAb (HB2 x anti-saporin)/(OKT10 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (HB2 x anti-saporin)/(OKT10 x anti-saporin) | CD7 + CD38 | T-ALL | Yes | | | [580] |
| Saporin | BsAb (HB2 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (HB2 x anti-saporin) | CD7 | T-ALL | Yes | | | [581] |
| Saporin | BsAb (OKT10 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (OKT10 x anti-saporin) | CD38 | T-ALL | Yes | | | [580] |
| Saporin | HB2-saporin | mAb (HB2) | CD7 | Lymphoma, T-ALL | Yes | Yes | | [582-584] |
| Saporin | BU12-saporin | mAb (BU12) | CD19 | B-LL, Burkitt's lymphoma | Yes | Yes | | [585-587] |
| Saporin | Rituximab/saporin-S6 | mAb (rituximab) | CD20 | NHL | Yes | | | [588] |
| Saporin | BsAb (4KB128 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (4KB128 x anti-saporin) | CD22 | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | BsAb (HD37 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (4KB128 x anti-saporin) | CD19 | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | BsAb (MB-1 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (4KB128 x anti-saporin) | CD37 | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | BsAb (4KB128 x anti-saporin)/(RFB9 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (4KB128 x anti-saporin)/(RFB9 x anti-saporin) | CD22 | Lymphoma, CLL | Yes | Yes | Phase I | [590] |
| Saporin | BsAb (4KB128 x anti-saporin)/(HD6 x anti-saporin)/saporin | Bispecific $F(ab')_2$ (4KB128 x anti-saporin)/(HD6 x anti-saporin) | CD22 | B-cell lymphoma | Yes | Yes | Phase I | [591] |
| Saporin | IB4/saporin-S6 | mAb (IB4) | CD38 (alpha-D-Galactopyranoside residues) | NHL | Yes | | | [592] |
| Saporin | Anti-B7-1-saporin | mAb (B7-24) | CD80 | Burkitt's lymphoma, Hodgkin's lymphoma | Yes | | | [593] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | Anti-CTLA-4 (83)-saporin (83-saporin) | scFv (83) | CD152 (Cytotoxic T-lymphocyte antigen-4, CTLA-4) | Transplantation tolerance, leukemia, EBV-positive B-cell lymphoblastoid | Yes | Yes | | [594-596] |
| Saporin | Anti-CTLA-4 (40)-saporin (40-saporin) | scFv (40) | CD152 (Cytotoxic T-lymphocyte antigen-4, CTLA-4) | Transplantation tolerance, EBV-positive B-cell lymphoblastoid | Yes | Yes | | [594, 595] |
| Saporin | Anti-CTLA-4 (67)-saporin (67-saporin) | scFv (67) | CD152 (Cytotoxic T-lymphocyte antigen-4, CTLA-4) | Transplantation tolerance, leukemia | Yes | | | [596] |
| Saporin | ATG-saporin-S6 | Antithymocyte globulin (ATG) | Thymocyte | Lymphoma, leukemia | Yes | | | [597] |
| Saporin | HD6-saporin | mAb (HD6) | CD22 | Lymphoma, B-CLL | Yes | | | [598] |
| Saporin | HD39-saporin | mAb (HD39) | CD22 | Lymphoma, B-CLL | Yes | | | [598] |
| Saporin | HD37-saporin | mAb (HD37) | CD19 | B-cell lymphoma | Yes | | | [598] |
| Saporin | Saporin-EGF (SE) | EGF | EGFR | Breast cancer, sarcoma, adenocarcinoma, cervical cancer | Yes | Yes | | [599-602] |
| Saporin | SA2E | EGF | EGFR | Breast cancer | Yes | Yes | | [599-601] |
| Saporin | FGF-SAP | FGF | FGFR | Melanoma, teratocarcinoma, neuroblastoma | Yes | Yes | | [603] |
| Saporin | FGF2-SAP | FGF-2 | FGFR | Bladder cancer | Yes | | | [604] |
| Saporin | bFGF-saporin | bFGF | bFGFR | Prostate cancer | Yes | Yes | | [605] |
| Saporin | ch25A11-Sap | mAb (ch25A11) | CUB domain-containing protein 1 (CDCP1) | Prostate cancer | Yes | Yes | | [606] |
| Saporin | hJ591-saporin | mAb (hj591) | Prostate-specific membrane antigen (PSMA) | Prostate cancer | Yes | Yes | | [607] |
| Saporin | Ep2-saporin | mAb (Ep2) | Proteoglycan, p250 | Melanoma | Yes | | | [608] |
| Saporin | ML30-saporin | mAb (ML30) | Heat shock protein 65 kDa (HSP65) | Leukemic monocyte lymphoma, pancreatic cancer | Yes | Yes | | [609, 610] |
| Saporin | 48-127/saporin-S6 | mAb (48-127) | gp54 | Bladder cancer | Yes | | | [379] |
| Saporin | Anti-ALCAM/CD166 scFv-saporin | scFv (I/F8) | CD166 (activated leukocyte cell adhesion molecule, ALCAM) | SCLC, ovarian cancer | Yes | | | [611] |
| Saporin | 7E4B11-saporin | mAb (7E4B11) | RPTPβ | Astrocytic tumor, glioblastoma | Yes | Yes | | [612] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | Ber-H2-Saporin | mAb (Ber-H2) | CD30 | Hodgkin's lymphoma, anaplastic large-cell lymphoma(ALCL) | Yes | Yes | Phase I | [374, 613-616] |
| Saporin | Sap-ac-LDL | Acetylated LDL | Rat scavenger receptor | Immunolesioning (microglia) | Yes | | | [617, 618] |
| Saporin | Anti-basigin-2-saporin | mAb (anti-basigin-2) | Human basigin-2 (CD147) (EMMPRIN) | Ovarian cancer | Yes | | | [619] |
| Saporin | M290-SAP | mAb (M290) | CD103 | Organ allograft rejection and GVHD | Yes | Yes | | [620] |
| Saporin | Anti-ChAT IgG-saporin | mAb (anti-ChAT) | Choline acetyltransferase (ChAT) | Parkinson's and schizophrenia | | Yes | | [621-623] |
| Saporin | Anti-DAT-saporin | mAb (anti-DAT) | Dopamine transporter (DAT) | Immunolesioning (dopaminergic neurons) | | Yes | | [624] |
| Saporin | Anti-DBH-saporin | mAb (anti-DBH) | Dopamine beta-hydroxylase (DBH) | Immunolesioning (noradrenergic neurons) | | Yes | | [625-627] |
| Saporin | Anti-SERT-SAP | mAb (anti-SERT) | Serotonin reuptake transporter (SERT) | Immunolesioning (serotonergic neurons) | Yes | Yes | | [628] |
| Saporin | Bombesin-SAP | Bombesin | Gastrin-releasing peptide receptor (GRPR) | Immunolesioning (GRPR+ neurons) | Yes | Yes | | [629, 630] |
| Saporin | CCK-saporin | CCK (cholecystokinin) | Cholecystokinin type 2 receptor ($CCK_2$) | Immunolesioning (CCK+ neurons) | | Yes | | [631] |
| Saporin | CRF-SAP | CRF (corticotropin-releasing factor) | CRF receptor | Immunolesioning (CRFR+ cells) | Yes | Yes | | [632, 633] |
| Saporin | CTB-SAP | CTB (cholera toxin B-subunit) | GM1 ganglioside | Immunolesioning (paraplegia) | | Yes | | [634] |
| Saporin | Dermorphin-saporin (MOR-SAP) | Dermorphin | Mu opioid receptor (MOR) | Immunolesioning (MOR+ neurons) | | Yes | | [631] |
| Saporin | Galanin-saporin (Gal-sap) | Galanin | Galanin-1 receptor (GalR1) | Immunolesioning (GalR1+ neurons) | | Yes | | [635] |
| Saporin | GAT1-saporin | IgG (GAT1) | GABA-transporter-1 | Immunolesioning (MSDB neurons), Alzheimer's disease | | Yes | | [636] |
| Saporin | Lep-SAP | Leptin | Leptin receptor | Immunolesioning (leptin receptor+ neuons) | | Yes | | [637, 638] |
| Saporin | Anti-Mac-1-SAP | mAb (anti-Mac-1) | CD11b (Mac-1) | Immunolesioning (Mac-1+ neuons, microglia) | Yes | Yes | | [639-642] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | ME20.4 IgG-saporin | mAb (ME20.4) | Primate p75 low-affinity neurotrophin receptor (p75NTR) | Immunolesioning (p75NTR+ neuons) | | Yes | | [643, 644] |
| Saporin | UF008/SAP | IgG (UF008) | Melanopsin | Immunolesioning (intrinsically photo-sensitive retinal ganglion cells, ipRGCs) | Yes | Yes | | [645, 646] |
| Saporin | NK3-SAP | Neurokinin-3 (NK3) | Neurokinin-3 recep-tor (NK3R) | Immunolesioning (NK3R+ neuons) | | Yes | | [647] |
| Saporin | NPY-SAP | Neuropeptide Y (NPY) | Neuropeptide Y receptor (NPYR) | Immunolesioning (NPYR+ neuons) | | Yes | | [648, 649] |
| Saporin | OXY-SAP | Oxytocin | Oxytocin receptors (OXYR) | Immunolesioning (OXYR+ neuons) | Yes | Yes | | [650] |
| Saporin | Substance P-saporin | Substance P | Neurokinin-1 recep-tor (NK1R) (Sub-stance P receptor) | Immunolesioning (NK1R+ neurons), hyperalgesia | | Yes | | [651-653] |
| Saporin | Hypocretin-saporin | Hypocretin (orexin) | Hypocretin-2 recep-tor | Narcolepsy (parval-bumin and choliner-gic neurons) | | Yes | | [654] |
| Saporin | TEC-T4-saporin | mAb (TEC-T4) | CD4 | T cells | Yes | | | [655] |
| Saporin | MB-1 x anti-sap-1/saporin | Bispecific mAb (MB-1 x anti-sap-1) | CD37 | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | OKT10-saporin | mAb (OKT10) | CD38 | T-cell ALL, lympho-cytes, macrophages | Yes | Yes | | [584] |
| Saporin | Campath-1-saporin | mAb (Campath-1) | CD52 | GVHD, myeloid cells | Yes | Yes | | [656] |
| Saporin | TEC IgM-SAP | mAb (TEC IgM) | Immunoglobulin heavy chain | Burkitt's lymphoma | Yes | | | [657] |
| Saporin | 8A-saporin 6 | mAb (8A) | 8A plasma cell-associated antigens | Multiple myeloma, Burkitt's lymphoma | Yes | | | [658] |
| Saporin | 62B1-saporin | mAb (62B1) | 62B1 plasma cell-associated antigens | Multiple myeloma, Burkitt's lymphoma | Yes | | | [658] |
| Saporin | 3BIT (BU12-saporin / OKT10-saporin + 4KB128-saporin) | mAb (BU12) / (OKT10) / (4KB128) | CD19 + CD22 + CD38 | Burkitt's lymphoma | Yes | Yes | | [659] |
| Saporin | BU12-saporin / OKT10-saporin | mAb (BU12) / (OKT10) | CD19 + CD38 | Burkitt's lymphoma | Yes | Yes | | [586] |
| Saporin | HB2-saporin / OKT10-saporin | mAb (HB2) / (OKT10) | CD7 + CD38 | T-cell ALL | Yes | Yes | | [584] |
| Saporin | B3/25-SO6 | mAb (B3/25) | TfR | Leukemia | Yes | | | [660] |
| Saporin | LAM3/saporin | mAb (LAM3) | M5b leukemia anti-gen | Acute non-lymphoid leukemia (ANLL) | Yes | | | [610, 661] |
| Saporin | Tf-saporin | Transferrin | TfR | Prostate cancer | Yes | | | [529] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | uPA-SAP | uPAcs (urokinase-type plasminogen activator) | Urokinase receptor | Lymphoma | Yes | | | [662] |
| Saporin | 11A8-saporin | mAb (11A8) | bFGFR | Ovarian cancer | Yes | Yes | | [663] |
| Saporin | Anti-CD8-saporin | mAb (anti-CD8) | CD8 | T-cell lymphoma | Yes | | | [655] |
| Saporin | HBEGF-saporin | HB-EGF | EGFR | Breast cancer, bladder cancer, melanoma, leukemia, colon cancer, renal cancer, ovarian cancer, prostate cancer, non-small cell lung cancer (NSCLC), brain cancer | Yes | | | [664] |
| Saporin | HBEGF-$L_{22}$-saporin | HB-EGF | EGFR | Breast cancer, bladder cancer, melanoma, leukemia, colon cancer, renal cancer, ovarian cancer, prostate cancer, non-small cell lung cancer (NSCLC), brain cancer | Yes | Yes | | [664] |
| Saporin | B-B10-saporin | mAb (B-B10) | CD25 (IL-2 receptor) | GVHD | Yes | | | [665] |
| Saporin | W6/800E6-SAP | mAb (W6/800E6) | HER2 | Breast cancer | Yes | | | [666] |
| Saporin | W6/900H1-SAP | mAb (W6/900H1) | HER2 | Breast cancer | Yes | | | [666] |
| Saporin | H2-$D^d$-saporin | H2-$D^d$ MHC class I tetramer | T-cell receptor (TCR) | diabetes mellitus, CD8+ T cells | Yes | | | [667] |
| Saporin | 2F8-saporin | mAb (2F8) | CD163 (SR-A) | Ovarian cancer | Yes | Yes | | [668] |
| Saporin | Insulin-saporin (saporin insulin complex, SIC) | Insulin | Insulin receptor | Ovarian cancer, hepatocellular carcinoma | Yes | | | [669] |
| Saporin | B-B2-saporin | mAb (BB2) | Myeloma antigen | Multiple myeloma | Yes | | | [670] |
| Saporin | B-B4-saporin | mAb (BB4) | Myeloma antigen | Multiple myeloma | Yes | | | [670] |
| Saporin | Anti-epithelial antigen-saporin 6 | mAb (anti-epithelial antigen) | Epithelial antigen | Colon cancer, epidermoid carcinoma | Yes | | | [302] |
| Saporin | Anti-SA-1-saporin | mAb (anti-SA-1) | mAb (SA-1) (16/6 idiotype binding to DNA) | Systemic lupus erythematosus (SLE) | Yes | Yes | | [671] |
| Saporin | Anti-Id-saporin | mAb (anti-Id) | mAb (Anti-Id) (anti-lymphoma idiotype) | B-cell leukemia | Yes | Yes | | [672] |
| Saporin | HB6-1 x anti-sap-1/saporin | Bispecific mAb (HB6-1 x anti-sap-1) | κ-chain | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | M15-8 x anti-sap-1/saporin | Bispecific mAb (M15-8 x anti-sap-1) | μ-chain | Burkitt's lymphoma | Yes | | | [589] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | RFB-9 x anti-sap-1/saporin | Bispecific mAb (RFB-9 x anti-sap-1) | CD19 | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | WR17 x anti-sap-1/saporin | Bispecific mAb (WR17 x anti-sap-1) | CD37 | Burkitt's lymphoma | Yes | | | [589] |
| Saporin | LAM7/saporin | mAb (LAM7) | M5b leukemia antigen | Acute non-lymphoid leukemia (ANLL) | Yes | | | [610, 661] |
| Saporin | 62B8-saporin 6 | mAb (62B8) | 62B8 myeloma antigen | Multiple myeloma | Yes | | | [658] |
| Saporin | $F(ab')_2$-saporin/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/anti-CD2 | $F(ab')_2$ (anti-IgG) / mAb (anti-CD2) | CD2 | T-cell lymphoma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/anti-CD5 | $F(ab')_2$ (anti-IgG) / mAb (anti-CD5) | CD5 | T-cell lymphoma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/C11 | $F(ab')_2$ (anti-IgG) / mAb (C11) | CD45 | Hodgkin's lymphoma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/TEC-T4 | $F(ab')_2$ (anti-IgG) / mAb (TEC-T4) | CD4 | T-cell lymphoma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/HSR-3 | $F(ab')_2$ (anti-IgG) / mAb (HSR-3) | CD30 | Hodgkin's lymphoma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/8A | $F(ab')_2$ (anti-IgG) / mAb (8A) | 8A myeloma antigen | Burkitt lymphoma, multiple myeloma | Yes | | | [303] |
| Saporin | $F(ab')_2$-saporin/62B1 | $F(ab')_2$ (anti-IgG) / mAb (62B1) | 62B1 myeloma antigen | Multiple myeloma | Yes | | | [303] |
| Saporin | PlGF-2-saporin | Placental growth factor-2 (PlGF-2) | PlGF-2 receptor | Tumor neovascularization | Yes | | | [673] |
| Saporin | ATF-saporin | ATF (amino-terminal fragment of human urokinase) | Urokinase receptor | Metastasis | Yes | | | [674] |
| Saporin | Cetuximab-saporin | mAb (cetuximab) | EGFR | Colorectal cancer, prostate cancer, epidermoid carcinoma, breast cancer | Yes | | | [675, 676] |
| Saporin | Trastuzumab-saporin | mAb (trastuzumab) | HER2 | Breast cancer | Yes | | | [676, 677] |
| Saporin | 2H8/anti-GAM IgG-saporin | mAb (2H8) / IgG (anti-GAM IgG) | Tomoregulin | Prostate cancer | Yes | | | [678] |
| Saporin | By114/anti-IgG-saporin | mAb (By114) / IgG (anti-IgG) | Carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) | Pancreatic cancer | Yes | Yes | | [679] |
| Saporin | 6-22 IgG/anti-GAH IgG-saporin | mAb (6-22 IgG) / IgG (anti-GAH IgG) | Human aspartyl (asparaginyl) β-hydroxylase (HAAH) | Hepatocellular carcinoma | Yes | | | [680] |

**(Table 2) Contd….**

| Toxin | Immunotoxin | Ligand | Target antigen | Tumor/Disease | *In vitro* | *In vivo* | Clinical trial status | Ref. |
|---|---|---|---|---|---|---|---|---|
| Saporin | Anti-endosialin/anti-IgG-saporin | mAb (anti-endosialin) / IgG (anti-IgG) | Endosialin (CD248, tumor endothelial marker 1, TEM1) | Ewing's sarcoma, neuroblastoma | Yes | | | [681] |
| Saporin | Anti-TCblR-saporin | mAb (anti-TCblR) | CD320 (transcobalamin receptor, TCblR) | CML, colon cancer | Yes | | | [682] |
| Saporin | AF334-saporin | mAb (AF334) | Tumor endothelial marker 8 (TEM8) | Tumor neovascularization | Yes | | | [683] |
| Saporin | MRK16/anti-IgG-saporin | mAb (MRK16) / IgG (anti-IgG) | 170 kDa glycoprotein (gp170) | Colon cancer | Yes | | | [684] |
| Trichokirin | AT15E-TKR (AT15E-Trichokirin) | mAb (anti-Thy 1.2) (AT15E) | CD90.2 (Thy 1.2) | Leukemia | Yes | Yes | | [270] |
| Trichokirin | $F(ab')_2$-trichokirin/UCHT1 | $F(ab')_2$ (anti-IgG) / mAb (UCHT1) | CD3 | T-cell lymphoma | Yes | | | [303] |
| Trichosanthin | TCS-Hepama-1 (Hepama-1-trichosanthin) | mAb (Hepama-1) | Hepatoma-associated antigen 43 kDa glycoprotein | Hepatoma | Yes | Yes | | [685, 686] |
| Trichosanthin | p75-TCS (anti-p75-anti-mouse IgG-trichosanthin) | mAb (192) / IgG (anti-mouse) | Rat nerve growth factor (NGF) receptor (p75 receptor) (p75NTR) | Immunolesioning (cholinergic basal forebrain neurons) | Yes | | | [574] |
| Trichosanthin | CMU15—TCS | mAb (CMU15A) | Lung cancer antigen | Lung cancer | Yes | Yes | | [687, 688] |
| Trichosanthin | TCS-Ng76 | mAb (Ng76) | Melanoma antigen | Melanoma | Yes | | | [689] |
| Trichosanthin | EGF-TCS | EGF | EGFR | Hepatocellular carcinoma | Yes | Yes | | [690, 691] |
| Trichosanthin | EGF-TCSredlk | EGF | EGFR | Hepatocellular carcinoma | Yes | Yes | | [692] |

Regrettably, in many cases this combination is not sufficient for a complete remission. Novel chemotherapeutics such as kinase inhibitors [59] and biological molecules such as antibodies [60] essentially improve the treatment of particular cancer entities. While kinase inhibitors are highly potent in suppressing cellular proliferation, antibodies are in particular characterized by their specificity for target cells. Targeted toxins combine the idea of tumor targeting and potent cytotoxicity in a single molecule. Thus, these molecules can be considered as an important addendum to complement the traditional troika. However, it must be stated that a promising therapeutic approach is finally characterized by its clinical success, but only a few targeted toxins have so far been approved by the Food and Drug Administration of the U.S., only one of them contains a protein-based toxin (denileukin diftitox) [61] and none of them is composed of a RIP. Nevertheless, targeted toxins containing RIPs are known from a number of clinical trials and a very large number of preclinical studies, indicating the great expected potential of this class of targeted toxins. Therefore, further research is needed to optimize current developments and to bring RIP-based anti-tumor drugs into the clinical routine. Although Moolten & Cooperband described as early as in 1970 the selective destruction of target cells by diphtheria toxin which was specifically linked to antibodies directed against specific antigens on the surface of tumor cells [62], the main obstacles for protein-based targeted toxins are still unsolved, which includes expensive production, unstable proteins and short biological half-life, immunogenicity and insufficient endosomal escape. Hundreds of research groups in the world are working on these problems, a substantial number of fruitful ideas have been published to date and the techniques to investigate and to manipulate such molecules are incredible compared to 1970 so that we can be confident that we must not wait further 40 years until targeted toxins will have their breakthrough.

## Molecular Aspects and Mechanisms in Targeted Toxin Therapy

Although the ultimate goal in a targeted tumor therapy is to kill the tumor cells, the modality of cell death must not be underestimated. Uncontrolled cell killing can result in colliquation, tyromatosis or coagulative necrosis, which may finally end up in causing life threatening or highly degenerative situation for the organism affected. On the contrary, apoptosis is a strictly controlled process for cell death. It can be induced by intracellular and/or extracellular signals resulting in systematic cell degradation with no damage of neighboring cells. While it is a commonly occurring process in

numerous cells on a daily basis, it may be impaired in tumor cells [63].

A similar process for cellular degradation is autophagy which involves the activity of lysosomal machinery which digests different cellular organelles. It is a process dependent on internal or external cellular environment and may lead to either cell death or the promotion of cellular survival [64]. Apoptosis and autophagy are stimulated or suppressed by similar pathways. The way a cell responds to these pathways determines its survival or death (this has been extensively reviewed in [65]). In general, the toxin's primary target such as the ribosomal RNA for RIPs is not directly involved in necrosis, apoptosis or autophagy, but these targets are involved in vital cellular processes. It seems natural to assume that the interference with vital functions results in a series of events that finally trigger the apoptotic cascade [66], but this is not true for all cases. In case of saporin, the induction of apoptosis also occurs before protein synthesis inhibition takes place [67]. Apart from this, in numerous reports there is a discrepancy in the exact mechanism in case of similar parameters studied. While in some cell lines apoptosis was indicated the same could not be confirmed in others. This also implies that the cellular response to targeted toxins is a multifaceted complex mechanism. Therefore, the choice of the toxin is a factor that must be given optimal thought in the design of targeted toxins.

## Drug Delivery Technologies Employed in Targeted Toxin Therapy

Carrier-based drug delivery systems have been widely exploited for the targeted delivery of toxins to the tumors. Commonly used drug targeting systems include nanoparticles, liposomes, virosomes, carbon nanotubes, microspheres, nanofibers amongst others [68-70]. A summary of the carrier and non-carrier based systems is shown in Fig. **3**. Despite the difficulty in formulation and the need for a more thorough stability and interaction assessment, the use of a carrier-based approach has distinctive advantages. Carriers help in a more specific ligand attachment increasing the specificity for the delivery of cargo. Increasing the circulatory time as in case of liposomal nanocarriers was of advantage for the delivery of cholera toxin, and despite its utility for adjuvant effects, the strategy has potential for its application in tumor therapy as well. A classical utilization of the liposomal drug delivery system was the delivery of gelonin [71]. It was delivered to the cytoplasm of TLX5 lymphoma cells most effectively by phosphatidylserine vesicles. This formulation could also successfully inhibit the protein synthesis in XC cells (rat fibroblasts transformed by *Rous sarcoma* virus) and phytohemagglutinin-stimulated CBA mouse lymphocytes. Phosphatidylcholine could only show the transport facility after addition of cholesterol to the cells. Addition of mixed bovine brain gangliosides in the following order phosphatidylcholine/cholesterol/gangliosides (5: 5: 1) escalated the effectiveness as well [71, 72]. Tumor targeted RIPs may take advantage of nanoparticulate drug delivery systems for intracellular targeting.

In the same context, a generation-4 polyamidoamine (PAMAM) dendrimer induced cellular uptake and intracellular release by facilitating the endocytic uptake of RIPs. The use of photochemical internalization (PCI) technology could increase the effectiveness of free RIPs and PAMAM-RIPs [73]. After PCI treatment, PAMAM-RIP facilitated internalization as well as nuclear entry. Albeit this being a negative outcome, the use of ER signaling could in turn be used to avoid this side effect and elicit a site specific response. The use of nanocarriers, liposomes, aptamers or dendrimeric structures may be helpful in the targeted delivery of the toxins. They surely facilitate the efficacy by either resulting in multivalence or providing a dual component delivery in a single system.

## Efficacy Enhancers in Targeted Toxin Therapy

In the past decade, a number of strategies have been attempted to circumvent the problems associated with immunogenicity, vascular leak syndrome and other off-target effects that are associated with targeted toxin therapy. Conventionally, the use of certain chemicals has been employed, which led to an elevation of the endosomal pH, thereby protecting the toxin from lysosomal enzyme degradation. Another strategy involved the use of pore forming agents (Fig. **4**). Use of these components certainly helped in im-

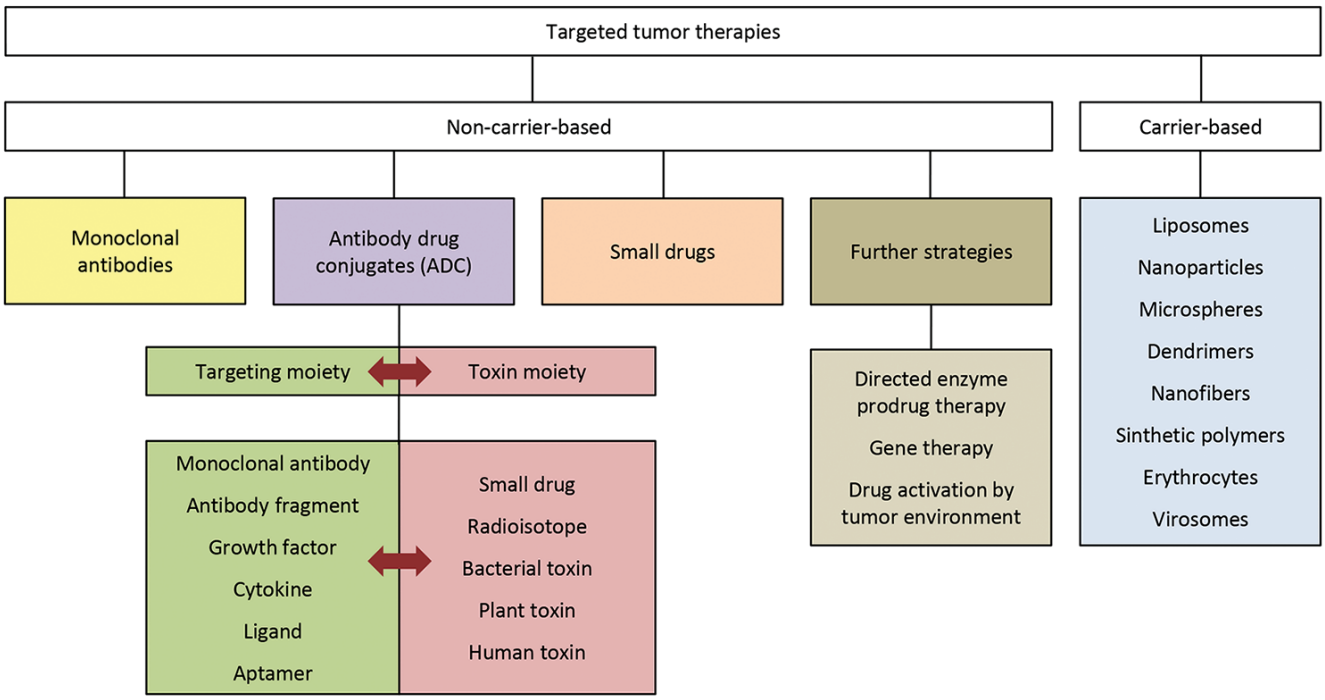


**Fig. (3).** A classification chart summarizing the carrier or non-carrier based approaches for targeted tumor therapy. While targeted toxins fall under the non-carrier based approach, toxins may also be incorporated in inert carriers for better stability.

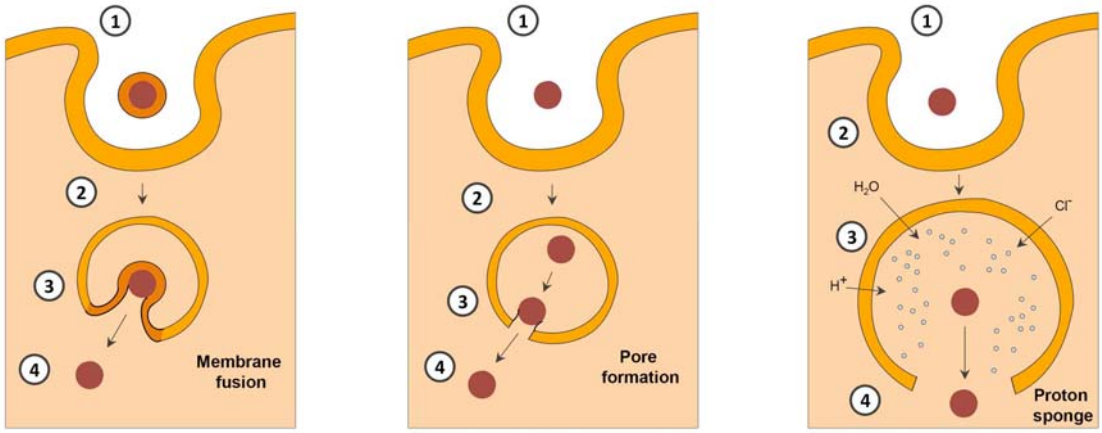


**Fig. (4).** A mechanistic description of the three widely known phenomena for the endosomal escape of molecules. Past internalization the toxin release may be facilitated *via* membrane fusion, pore formation or proton sponge effect. Table **3** describes in detail all the compounds that facilitate these effects for improving the efficacy of targeted toxins.

proving the efficacy but their proof in preclinical and clinical studies is still limited [74-78]. The details for other compounds including organic and inorganic substances, synthetic peptides and compounds of natural origin are detailed in Table **3**. In an interesting study, the anti-tumoral effects of anti-CD5 immunotoxins, which were constructed using a monoclonal antibody Fab fragment linked to native ricin A-chain or partially deglycosylated ricin A-chain, were examined in combination with the enhancer monensin conjugated to human serum albumin and injected intraperitoneally. In this case, 90% of the tumor cells were killed. This potentiating effect was observable even at a 5% monensin saturation level. The authors were able to successfully inhibit the effect by injecting the unconjugated antibody.

These results show that the therapeutic efficacy of immunotoxins can be very well improved by following a pre-defined and optimized therapeutic regime [79]. Monensin is one of the compounds with proven efficacy. In the recent past, an even higher synergy has been observed by the concomitant use of saponins and plant RIPs which is the basis for the next section.

### Saponins in Targeted Toxin Therapy

In our research group, we have been extensively working with the use of certain structurally specific triterpenoids *viz.* saponins. These compounds have shown tremendous potential in enhancing the effectiveness of targeted toxins; mainly plant type I RIPs saporin and dianthin (Fig. **5**) [80, 81]. Saponins are generally classified as triterpenoidal or steroidal, based on the aglycone backbone. In general, the saponins have a sugar chain attached at either the C-3 or C-17 position (monodesmosidic saponins), or on both positions (bisdesmosidic saponins). In recent studies, the concomitant use of saponins from *Saponaria officinalis* L. and *Gypsophila paniculata* L. has been successful in synergistically enhancing the toxicity of saporin-EGF and dianthin-EGF [30]. Evaluation of the molecular mechanism revealed that the toxin was internalized *via* receptor mediated internalization, thereafter the saponins (which were used at a concentration far below their membrane pore forming concentrations) lead to an enhanced endosomal escape of the toxin, which in turn resulted in apoptosis. The efficacy of saponins to facilitate rapid cell death, when administered in unison with the targeted toxins was further confirmed in a real-time cytotoxicity evaluation. Cell death was observed as a fall of the impedance signal (representing the number of living cells) within the first 12 h of incubation of the toxin and the saponins, while the toxin alone requires a 10,000-fold higher concentration to induce cell death after a period of nearly 48 h of incubation. It is pertinent to mention here that the saponins were used at a concentration that has no effect on its own [74-76, 82-84].

The structural features of saponins that are highly desirable for their enhancing effects have been studied extensively. It is now established that bisdesmosidic triterpenoidal saponins, which have a gypsogenin or quillaic acid backbone with a glucuronic acid at C-3 position are most effective. Moreover, there are further specific structural and sugar chain requirements that lead to a relatively small number of saponins, which show effectiveness as synergistic enhancers. As already detailed, for exerting cytotoxicity, the release of toxin in the cytosol is a very important step. This process is however very feeble in case of internalized RIPs. Interestingly, Weng et al. demonstrated that saponins which are also biosynthesized by *Saponaria officinalis* L., can in a very specific manner facilitate the cytosolic transfer of toxin without affecting the plasma membrane integrity. This effect mainly takes place in late endosomes and lysosomes at a pH range between 4-5.5. A strong binding affinity for saponins with RIPs using surface plasmon resonance was also verified and the combination of the targeted toxin and saponin was validated for its effectiveness *in vivo* in a syngeneic mouse tumor model [85]. Although using saponins or for that matter any toxicity enhancer is a novel approach for improving the effectiveness of targeted toxins, there are certain limitations associated with this strategy more importantly from a clinical perspective. Any clinical application involving the use of multiple components is always a practical and a regulatory problem. This problem in case of saponins or other enhancers can only be circumvented by the use of a drug carrier system, which either encompasses the two components together or either of the two components form a part of the delivery matrix.

## OUTLOOK AND CONCLUSION

The initial hope for immunotoxin-based therapy in the treatment of cancer was their perceived role as magic bullets functioning as a cure for solid tumors and blood borne malignancies [86]. Since the 1990s, clinical studies have clearly shown that the targeted toxin therapy works as a good supplement to the existing chemotherapeutic agents [87]. The combination of chemo- and immunotherapy is manifolds better than the effectiveness of either of them alone. This when accompanied with the combined use of enhancers would surely give the clinicians more advantage in treating the patients effectively. There are numerous facets to targeted toxin therapies and as summarized by Chandramohan et al. [88], the therapeutic success requires selective killing, absence of side effects or nonspecific toxicity, which should be further juxtaposed with

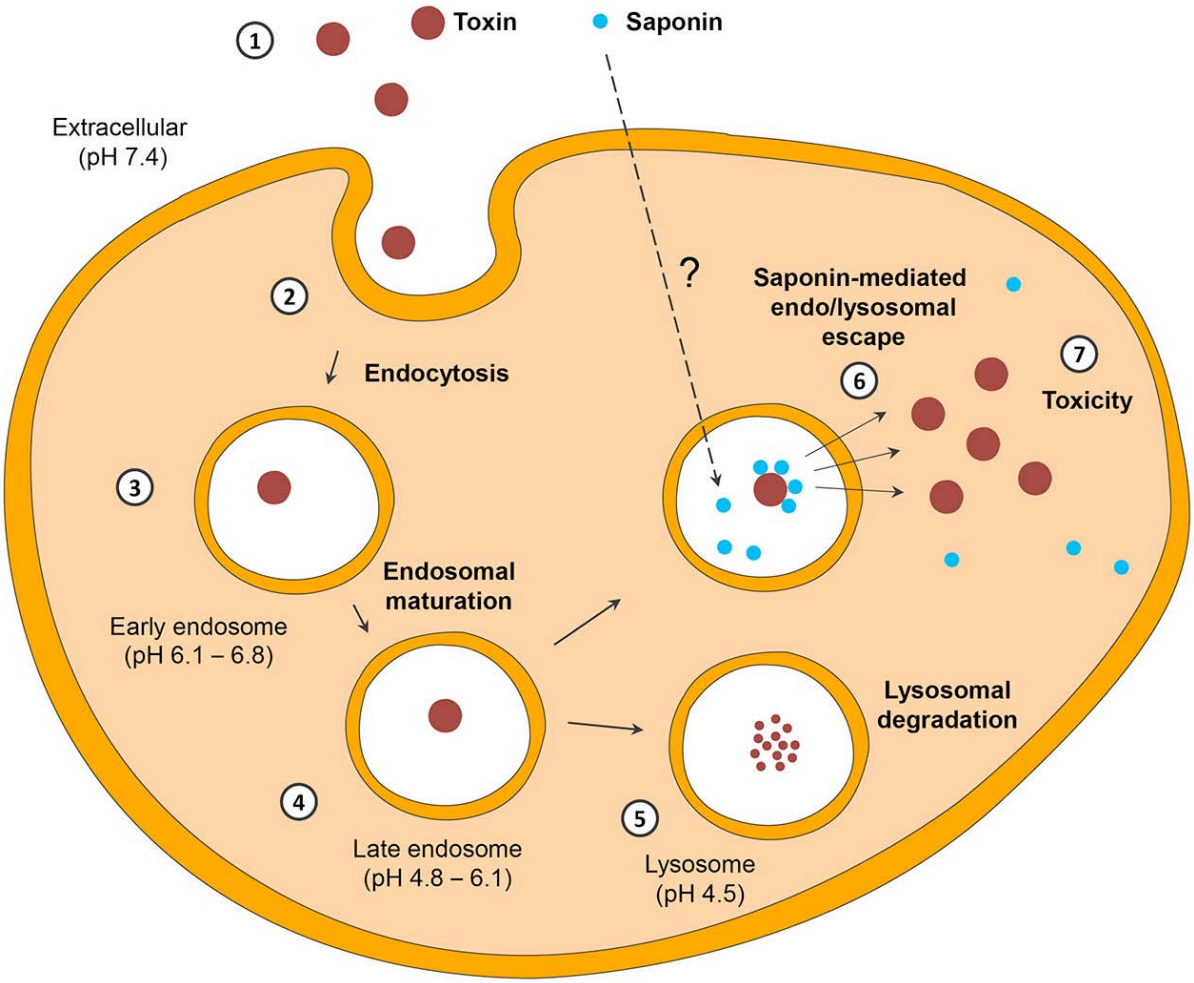


**Fig. (5)**. A schematic description for the efficacy enhancement of certain plant type I RIPs using triterpenoidal saponins. 1. The toxin reaches the cell 2. Internalization and formation of endosomal vesicles, 3. Maturation of the endosomal vesicles along with the entrapped toxin, 4. Late endosome formation. 5. The toxin undergoes lysosomal degradation and thus the toxic effect is not elicited. 6. Particular saponins accumulates inside the endo/lysosomes by unknown mechanisms. The presence of saponins faciliates the endo/lysosomal release of the toxin in a pH dependent manner. 7. The toxin induces cell death inside the cytosol *via* apoptosis.

successful delivery of the immunotoxin to tumor cells. Another important aspect for a clinical success is the designing of targeted toxin. This should be done in such a way that the production of anti-toxin antibodies is minimized in an ideal case. Most of the target receptors are ubiquitous and therefore, a bystander effect of the targeting strategy into normal tissues in most cases is unavoidable. It is in such instances that the use of a targeted toxin enhancer as described in Table **3** can certainly come to rescue. Since use of such strategy minimizes the dosage and therefore the accompanying side effects, the target specific cell killing is limited to the amount of toxin molecules available.

Another important aspect is the fact that most of the disseminated tumors are highly heterogeneous. This is further complicated by the variations in the receptor expression levels with progression of tumor into the different stages of growth [89]. It is in such cases that a "cocktail therapy" could be highly effective and beneficial [90]. In the past, the targeted toxins have shown limited success independently and it could be imagined that for a higher efficacy, a combination of a small drug with targeted toxins, administered concomitantly, may minimize the side effects of either of them, with an increased effectiveness. In addition, another strategy could be the use of a combination of two or more targeted toxins as shown by a joint application of anti-CD19 and anti-CD22 immunotoxins (Combotox) [91] or multiple receptor targeting by aptameric configurations of the toxins making them more specific to different receptor types, overexpressed in the tumor that is being targeted. The future for such an approach has tremendous potential with the recent advancement in high-throughput screening techniques and the growing importance of personalized medicine in case of tumor treatment.

Furthermore, development of bi-specific and tri-specific therapeutic antibodies would surely add to the armor of the clinicians handling targeted toxins in tumor therapy [92, 93]. It can be foreseen that a cargo of toxin, with multiple targeting ligands would be highly beneficial, not only in solid tumors but in case of disseminated and metastasized tumors as well. The future of targeted toxin therapies appears to be even more promising than within the previous decade; this is mainly ascribable to the tremendous advancements in the biotechnological tools and an unprecedented growth in the field of proteomics and genomics. The possibility of identification and procurement of inactive mutants and humanized or human toxins, which can be further modified as targeted toxins opens up

**Table 3. A detailed list of all the efficacy enhancers employed in the improvement of toxin efficacy and enhancement of endosomal escape.**

| Efficacy Enhancers | Origin | Factor | Site of Action | Application | Ref. |
|---|---|---|---|---|---|
| *Lysosomotropic amines* | | | | | |
| Ammonium chloride | Inorganic | 6700 | Endosomes | Immunotoxins (RTA) | [693, 694] |
| Methylamine | Organic | 13,300 | Endosomes | Immunotoxins (RTA) | [693] |
| Dimethylamine | Organic | 3300 | Endosomes | Immunotoxins (RTA) | [693] |
| Trimethylamine | Organic | 80 | Endosomes | Immunotoxins (RTA) | [693] |
| Amantadine | Organic | 1180 | Endosomes | Immunotoxins (RTA) | [693, 695] |
| Chloroquine | Organic | 2500 | Endosomes | Immunotoxins (RTA, Gel) | [693, 696] |
| Lipopolyamines | Organic | 10 - 250 | Endosomes | Immunotoxins (Sap) | [697] |
| β-Glycylphenyl-naphthylamide (GPN) | Organic | 10 | Endosomes | Immunotoxins (PE) | [698] |
| Quinacrine | Organic | 15 | Endosomes | immunotoxins (Gel) | [696] |
| *Carboxylic ionophores* | | | | | |
| Monensin | Organic | 50,000 | Lysosomes | Immunotoxins (RTA, Gel) | [693, 696, 699] |
| Grisorixin | Organic | 25,000 | Lysosomes | Immunotoxins (RTA) | [693] |
| Lasalocid | Organic | 33,000 | Lysosomes | Immunotoxins (RTA) | [693] |
| Nigericin | Organic | 6700 | Lysosomes | Immunotoxins (RTA) | [693] |
| *Calcium channel antagonists* | | | | | |
| Verapamil | Organic | 170 | Lysosomes or other vesicular compartments | Immunotoxins (RTA, PE, Gel) | [696, 698, 700] |
| Diltiazem | Organic | 10, 40 | Lysosomes or other vesicular compartments | Immunotoxins (PE) | [698] |
| Methoxyverapamil (D-600) | Organic | 40 | Lysosomes or other vesicular compartments | Immunotoxins (PE) | [698] |
| Varapamil analogues | Organic | 2 - 70 | Lysosomes or other vesicular compartments | Immunotoxins (RTA, PE) | [700] |
| Perhexiline | Organic | 10 - 2000 | Lysosomes or other vesicular compartments | Immunotoxins (RTA) | [701] |
| SR 33557 | Organic | 540 | Lysosomes or other vesicular compartments | Immunotoxins (RTA) | [702] |
| SR 33287 | Organic | 620 | Lysosomes or other vesicular compartments | Immunotoxins (RTA) | [702] |
| *Organic polymers* | | | | | |
| Polyethylenimine (PEI) | Organic polymer | From no-effect to effect | Lysosomes | Gene transfection | [703] |
| Poly(amidoamine)s (PAAs) | Organic polymer | 100 | Endosomes and lysosomes | Toxins (RTA, Gel, Sap), Gene delivery | [704-706] |
| Poly(propylacrylic acid) (PAAP) | Organic polymer | Significant increase | Endosomes | Gene transfection | [707] |

**(Table 3) Contd….**

| Efficacy Enhancers | Origin | Factor | Site of Action | Application | Ref. |
|---|---|---|---|---|---|
| *Fusogenic lipids* | | | | | |
| DOPE | Organic | Significant increase | Endosomes | Gene transfection, liposomes | [708] |
| CHEMS | Organic | Significant increase | Endosomes | siRNA delivery | [709] |
| Monoolein | Organic | Significant increase | Endosomes | DNA delivery, nanoparticles | [75] |
| *Other organic compounds* | | | | | |
| Retinoic acid | Organic | 10,000 | Golgi apparatus | Immunotoxins (RTA) | [710] |
| Cyclosporin A | Organic | 100 | Vesicular compartments | Immunotoxins (RTA) | [711, 712] |
| Brefeldin-A | Organic | 1000 | Golgi apparatus | Immunotoxins (RTA) | [713] |
| Bryostatin 1 | Organic | Significant increase | Cell signalling | Immunotoxins (PE) | [714] |
| Wortmannin | Organic | Significant increase | Endosomes and lysosomes | Immunotoxins (ETA, Sap, Gel) | [715] |
| Synthetic surfactants | Organic | Significant increase | Endosomes | Gene transfection, siRNA delivery, nanoparticles | [716, 717] |
| EHCO | Organic | Significant increase | Endosomes | siRNA delivery, nanoparticles | [718] |
| *Viruses and virus peptides* | | | | | |
| Adenovirus | Adenovirus | 10,000 | Endosomes, lysosomes or other vesicular compartments | Immunotoxins (PE, RTA, Sap, Gel), gene delivery | [719-721] |
| Penton base protein (adenovirus capsid protein) | Adenovirus | 100 | Endosomes and lysosomes | Immunotoxins (PE, Gel) | [722, 723] |
| Minor capsid protein VI | Adenovirus | From no-effect to effect | Endosomes | Nanoparticles | [724, 725] |
| KFT25 (N-terminus of Protein G) | Vesicular stomatitis virus | 10 - 20 | Lysosomes or other vesicular compartments | Immunotoxins (RTA, Dia) | [309, 528] |
| HA2 (hemagglutinin HA-2) | Influenza virus | 10 - 100 | Endosomes | Immunotoxins (RTA, Sap), gene transfer | [82, 726, 727] |
| HA2 / poly (L-lysine) (PLL) | Influenza virus | Significant increase | Endosomes | Gene transfer | [728] |
| HA23 | Influenza virus | 4 - 5 | Endosomes | Immunotoxins (RTA) | [729] |
| GALA | Synthetic peptide (HIV) | From no-effect to effect | Endosomes | Gene transfection, liposomes, nanoparticles | [726, 730, 731] |
| KALA | Synthetic peptide (HIV) | From no-effect to effect | Endosomes and other membranes | Gene transfection | [732] |
| KALA/polyethylenimine (PEI) | Synthetic peptide (HIV) | Significant increase | Endosomes and other membranes | Gene transfection | [733, 734] |
| INF-7 | Influenza virus | 100 | Endosomes | Gene delivery, siRNA delivery, liposomes | [735-737] |
| Tat (transcriptional activator Tat protein) | HIV | 3340 | Endosomes | DNA delivery, PNA delivery, liposomes, nanoparticles | [738-740] |
| gp41 | HIV | Significant increase | Endosomes | Gene delivery, siRNA delivery | [741] |
| gp41/polyethylenimine (PEI) | HIV | Significant increase | Endosomes | Gene delivery, siRNA delivery | [742] |
| L2 (minor capsid protein) | Papillomavirus | From no-effect to effect | Endosomes and other membranes | Proteins (GFP) | [743] |
| Major envelope protein (E) | West Nile virus | From no-effect to effect | Endosomes | Natural process | [744] |

**(Table 3) Contd….**

| Efficacy Enhancers | Origin | Factor | Site of Action | Application | Ref. |
|---|---|---|---|---|---|
| VP22 (structural protein VP22) | Herpes simplex virus | From no-effect to effect | Actin-mediated endosomes | DNA delivery, proteins (GFP) | [729] |
| Synthetic analogue of glycoprotein H (gpH) | Synthetic peptide (Herpes simplex virus) | 30 | Endosomes | Gene transfection, liposomes | [745] |
| PreS2-domain of hepatitis-B virus surface antigen (TLM) | Hepatitis-B virus | 2 - 20 | Endosomes or other vesicular compartments | Immunotoxins (Sap, Ang) | [600, 746, 747] |
| *Bacterial peptides* | | | | | |
| Listeriolysin O (LLO) | *Listeria monocytogenes* | Significant increase | Endosomes | DNA delivery, liposomes | [748, 749] |
| Pneumococcal pneumolysin (PLO) | Pneumococcos | From no-effect to effect | Endosomes | Toxins (Granzyme B) | [750] |
| Streptococcal streptolysin O (SLO) | Streptococcos | From no-effect to effect | Endosomes | Toxins (Granzyme B) | [750] |
| T-domain of diphtheria-toxin (DT) | *Corynebacterium diphtheria* | From no-effect to effect | Endosomes | Immunotoxins (DT) | [751] |
| T-domain of diphtheria toxin (DT) / poly(ethylenimine) (PEI) | *Corynebacterium diphtheria* | Significant increase | Endosomes | Gene transfection | [752] |
| Domain II of *Pseudomonas* exotoxin A (ETA) | *Pseudomonas aeruginosa* | From no-effect to effect | Endosomes and *trans*-Golgi network | Immunotoxins (PE) | [753] |
| REDLK | *Pseudomonas aeruginosa* | From no-effect to effect | Endoplasmatic reticulum | Immunotoxins (PE) | [754] |
| *Animal and human peptides* | | | | | |
| Penetratin (homeotic transcription protein Antennapedia, Antp) | *Drosophila melanogaster* | From no-effect to effect | Pinocytic and other vesicular compartments | PNA delivery | [755] |
| R6-Penetratin (with arginine residues) | Synthetic (*Drosophila melanogaster*) | 5 - 10 | Endosmes and other vesicular compartments | PNA delivery | [756] |
| EB1 (synthetic analog of penetratin) | Synthetic (*Drosophila melanogaster*) | Significant increase | Endosomes | siRNA delivery | [757] |
| hCT (9-32) (human calcitonin derived peptide 9-32) | Human | From no-effect to effect | Endosomes or other vesicular compartments | Natural process | [758, 759] |
| Fibroblast growth factor-1 (FGF-1) sequence | Human | From no-effect to effect | Endosomes | Natural process | [760] |
| Melittin | Bee venom | From no-effect to effect | Endosomes | Gene delivery | [726, 761] |
| Melittin/polyethylenimine (PEI) | Bee venom | Significant increase | Endosomes | Gene delivery, siRNA delivery | [762-764] |
| Human β3 integrin signal sequence | Human | From no-effect to effect | Endosomes | Natural process | [765] |
| Heavy chain of immunoglobulin G | *Caiman crocodylus* | Significant increase | Cell membrane | Liposomes | [766] |

**(Table 3) Contd….**

| Efficacy Enhancers | Origin | Factor | Site of Action | Application | Ref. |
|---|---|---|---|---|---|
| Transportan | Synthetic peptide (neuropeptide galanin + wasp venom peptide mastoparan) | From no-effect to effect | Endosomes or other vesicular compartments | Proteins (GFP, Strep) | [767] |
| Bovine prion protein (bPrPp) | Synthetic peptide (bobine prion) | From no-effect to effect | Cell membrane, macropinosomes | Nanoparticles | [768, 769] |
| KDEL | Signal sequence | 100 - 1000 | Endoplasmatic reticulum | Immunotoxins (RTA, PE) | [770, 771] |
| *Animal and human proteins* | | | | | |
| α-Interferon (INF) | Human | Significant increase | Cell signalling | Immunotoxins (RTA) | [772] |
| Perforin | Human | From no-effect to effect | Early endosomes | Immunotoxins (GzmB) | [773, 774] |
| Rituximab | Mouse/human chimeric mAb | 80 | Cell signalling | Immunotoxins (Sap) | [587] |
| *Plant saponins* | | | | | |
| *Saponinum album* | *Gypsophila paniculata* L. | 2,500,000 | Late endosomes and lysosomes | Immunotoxins (Sap) | [599, 775, 776] |
| SA-1641 | *Gypsophila paniculata* L. | Significant increase | Late endosomes and lysosomes | Immunotoxins (Sap, Dia) | [83, 84] |
| SA-1657 | *Gypsophila paniculata* L. | From no-effect to effect | Late endosomes and lysosomes | Immunotoxins (Sap) | [52] |
| *Saponaria* saponins | *Saponaria officinalis* L. | 10, 000 | Late endosomes and lysosomes | Immunotoxins (Sap) | [52] |
| SO-1861 | *Saponaria officinalis* L. | 1000 | Late endosomes and lysosomes | Immunotoxins (Sap, Dia) | [52] |
| *Quillaja* saponins | *Quillaja saponaria* Mol. | 1400 | Late endosomes and lysosomes | Immunotoxins (Sap) | [775] |
| *Plant proteins* | | | | | |
| Ricin B-chain | *Ricinus communis* L. | From no-effect to effect | Interalization/Cell signalling | Immunotoxins (RTA) | [777] |
| Ricin B-chain immunotoxin | *Ricinus communis* L. | 2 - 4 | Interalization/Cell signalling | Immunotoxins (RTA) | [778] |
| Ricin B chain (piggyback) | *Ricinus communis* L. | 2 - 6 | Interalization/Cell signalling | Immunotoxins (RTA) | [779] |
| *Synthetic peptides* | | | | | |
| Polyarginines | Synthetic peptide | Significant increase | Late endosomes, Golgi apparatus and endoplasmatic reticulum | DNA delivery, siRNA delivery, proteins (GFP) | [780-782] |
| Polylysines | Synthetic peptide | Significant increase | Endosomes | Gene transfection | [783] |
| Histidine 10 | Synthetic peptide | 7000 | Endosomes | Gene transfection | [784] |
| $(R\text{-}Ahx\text{-}R)_4$ | Synthetic peptide | From no-effect to effect | Late endosomes, Golgi apparatus and endoplasmatic reticulum | PNA delivery | [74, 785] |
| Poly(L-histidine) | Synthetic peptide | Significant increase | Endosomes | DNA delivery | [786, 787] |

**(Table 3) Contd….**

| Efficacy Enhancers | Origin | Factor | Site of Action | Application | Ref. |
|---|---|---|---|---|---|
| Sweet arrow peptide (SAP) | Synthetic peptide | Significant increase | Endosomes | Gene delivery, nanoparticles | [788] |
| Loligomer | Synthetic peptide | From no-effect to effect | Endosomes or other vesicular compartments | Peptide delivery, fluorescent probes | [789] |
| Amphiphilic model peptide | Synthetic peptide | From no-effect to effect | Endosomes or other vesicular compartments | Polar bioactive compounds | [790] |
| IRQ peptide | Synthetic peptide | Significant increase | Endosomes | siRNA delivery | [709] |
| $4_3$E peptide | Synthetic peptide | Significant increase | Endosomes and lysosomes | Gene transfection | [791] |
| pJVE | Synthetic peptide | 2 | Endosomes | Immunotoxins (Dia) | [309] |
| RAWA | Synthetic peptide | Significant increase | Endosomes and other membranes | Gene delivery | [792] |
| Nuclear localization signals | Synthetic peptide | 150 | Cytoplasmic entrapment, nuclear membrane | Gene transfection | [793] |
| SynB1 | Synthetic peptide | 6 | Endosomes and other membranes | Peptide delivery | [78, 794] |
| Pep-1 | Synthetic peptide | From no-effect to effect | Endosomes and other membranes | Peptide delivery, proteins (GFP, β-Gal) | [795] |
| *Physicochemical techniques* | | | | | |
| Photochemical internalization | Technique | 1000 | Endosomes | Immunotoxins (Sap, Gel), gene transfection, liposomes, nanoparticles | [796-798] |
| Ultrasound | Technique | 30 | Endosomes | Gene delivery, liposomes | [799, 800] |
| Plasmonic nanobubbles | Technique | 30 | Endosomes | Nanoparticles | [801] |
| Magnetic nanoparticles | Technique | From no-effect to effect | Endosomes | Gene transfection, siRNA delivery, nanoparticles | [76, 802] |

new vistas for tumor treatment. Recombinant DNA and expression techniques have reached a stage where a mutated version once identified to be effective, can be expressed and obtained under good manufacturing conditions in a quick succession. Recent advancements in the antibody-based therapeutics include the generation of bi-specific antibodies and bio-mimicking antibodies, while retaining selectivity these antibodies reportedly have a better efficacy. This surely adds to the repertoire of molecular biologists for reducing the incubation time during the drug development process.

## CONFLICT OF INTEREST

Declared none.

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