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IL-2 and Beyond in Cancer Immunotherapy

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The development of the T- and natural killer (NK) cell growth factor IL-2 has been a sentinel force ushering in the era of immunotherapy in cancer. With the advent of clinical grade recombinant IL-2 in the mid-1980s, oncologists could for the first time directly manipulate lymphocyte populations with systemic therapy. By itself, recombinant IL-2 can induce clinical responses in up to 15% of patients with metastatic cancer or renal cell carcinoma. When administered with adoptively transferred tumor-reactive lymphocytes, IL-2 promotes T cell engraftment and response rates of up to 50% in metastatic melanoma patients. Importantly, these IL-2-driven responses can yield complete and durable responses in a subset of patients. However, the use of IL-2 is limited by toxicity and concern of the expansion of T regulatory cells. To overcome these limitations and improve response rates, other T cell growth factors, including IL-15 and modified forms of IL-2, are in clinical development. Administering T cell growth factors in combination with other agents, such as immune checkpoint pathway inhibitors, may also improve efficacy. In this study, we review the development of T- and NK cell growth factors and highlight current combinatorial approaches based on these reagents.

Keywords: IL-2, IL-15, adoptive cellular therapy, T cells

IL-2: From Supernatant to Clinical Grade Therapy

The identification of IL-2 as a therapeutic agent began unwittingly in the mid-1960s when it was discovered that supernatants of antigen- or mitogen- activated leukocyte cultures contained a factor able to stimulate lymphocyte division (Gordon and MacLean 1965; Kasakura and Lowenstein 1965). By 1969, the term ''lymphokine'' had been coined (Dumonde and others 1969), and much research was dedicated to understanding the soluble factor or factors responsible (Dumonde and others 1969; Pick and Turk 1972; Chen and Di Sabato 1976). In 1976, Gallo and colleagues demonstrated that conditioned media from human lymphocytes contained this factor and could be used to maintain T cell cultures for over 9 months without the need for repetitive antigenic stimulation (Morgan and others 1976). This technique was quickly adapted to the culture of tumor-reactive T cells with sustained cytotoxic potential (Gillis and Smith 1977). These early studies led to the development of methods for enriching, purifying, and measuring this soluble factor (Farrar and others 1978; Gillis and others 1978; Shaw and others 1978; Watson and others 1979; Gillis and Watson 1980; Mier and Gallo 1980; Robb and others 1981; Stadler and others 1982), which would be named IL-2. Collectively, these advances allowed scientists to study this lymphocyte growth factor in greater depth.

In mice, both the persistence and antitumor efficacy of lymphocytes were greatly augmented upon injection of purified IL-2 (Cheever and others 1982, 1984; Donohue and others 1984). Furthermore, simply culturing lymphocytes *in vitro* with IL-2 could lead to the acquisition of ability to preferentially lyse tumor cells over healthy cells (Lotze and others 1981; Grimm and others 1982; Rayner and others 1985b). The effector cells mediating this tumor cytotoxicity were called lymphokine activated killer (LAK) cells and showed antitumor efficacy in preclinical models (Mazumder and Rosenberg 1984). These successes led to the evaluation of purified IL-2 in cancer and HIV-infected patients (Bindon and others 1983; Lotze and others 1984; Rayner and others 1985a). Although there was some evidence of biological activity, including toxicities, there were no clinical responses in the small number of patients treated.

In what was a critical milestone, the sequencing of the human IL-2 gene was reported in 1983 (Taniguchi and others 1983) and the murine IL-2 gene shortly thereafter (Kashima and others 1985). The cloning of IL-2 allowed the production of large quantities of purified recombinant IL-2 using *Escherichia coli* (Devos and others 1983; Taniguchi and others 1983; Lotze and others 1984; Wang and others 1984). Rosenberg and colleagues

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demonstrated that administration of recombinant IL-2 to mice mediated potent antitumor activity with regression of established pulmonary metastases and subcutaneous tumors (Lafreniere and Rosenberg 1985). In an initial clinical study reported in 1985, 20 patients with a variety of malignancies were treated with recombinant IL-2. This treatment resulted in the expansion of lymphoid populations but no clinical responses (Lotze and others 1985). An alternate clinical approach was suggested by experiments in mice showing that combining adoptive transfer of LAK cells with recombinant IL-2 was much more effective against tumor than either agent alone (Mule and others 1984, 1985, 1986; Lafreniere and Rosenberg 1985). While LAK cells had been evaluated clinically (Lotze and others 1980), these cells had never been coadministered to patients with recombinant IL-2. In the first human experience of LAK cells and recombinant IL-2 in patients with advanced cancer, 11 of 25 patients experienced objective responses defined as at least a 50% reduction in tumor volume and this included patients with metastatic melanoma, renal cell carcinoma, colon cancer, and lung adenocarcinoma (Rosenberg and others 1985). Among the responders was a patient with metastatic melanoma who experienced a complete response and has been disease free for 29 years (Rosenberg 2014). The conclusion that adding LAK cells improved IL-2 therapy was however complicated by the fact that a higher dose of IL-2 was used, as well as differences in the patient population. Therefore, in a subsequent study, Rosenberg and colleagues evaluated whether higher doses of IL-2 alone could be effective. In a small study of 10 patients, higher doses of IL-2 mediated clinical responses, including in 3 of 6 treated patients with metastatic melanoma (Lotze and others 1986a). These studies demonstrated for the first time that IL-2 administered as a single agent mediated antitumor efficacy in human patients with metastatic cancer.

An important remaining question was whether adoptively transferring LAK cells in addition to IL-2 therapy could improve efficacy. Therefore, Rosenberg and colleagues compared the administration of high-dose IL-2 alone versus high-dose IL-2 and LAK cells in metastatic melanoma and renal cell carcinoma patients. In a clinical trial with 181 patients randomized to two groups, 16 of 91 patients (18%) with IL-2 alone had objective responses, while 24 of 90 patients (24%) with IL-2 and LAK cells had objective responses (Rosenberg and others 1993). There was not a statistically significant difference in overall survival between patients receiving IL-2 versus IL-2 and LAK cells. However, there was a trend toward improved overall survival in the subset of metastatic melanoma patients that received IL-2 and LAK cells versus IL-2 alone. These results did not justify the addition of LAK cells to IL-2 therapy, particularly as the LAK cells could not be given as an off-the-shelf reagent. Subsequently, 2 other significant trials evaluated the efficacy of IL-2 alone. In 1 trial published in 1995, of 255 patients with renal cell carcinoma, roughly 15% of patients achieved objective responses with about one third of these being complete responses (Fyfe and others 1995). Similar response rates were reported in 1999 in a trial of over 270 patients with metastatic melanoma (Atkins and others 1999). Compared with other therapies available at the time, responses obtained with recombinant IL-2 were remarkable in their durability, with some patients achieving complete responses ongoing after 10 years (Rosenberg 2014). Notably, IL-2 administration in patients is associated with increased frequencies and activation of lymphocytes within the tumor (Cohen and others 1987; Swisher and others 1991). The Food and Drug Administration (FDA) approved IL-2 for the treatment of renal cell carcinoma in 1992 and metastatic melanoma in 1998 (Rosenberg 2014).

Receptors in the IL-2 Cytokine Family

IL-2 acts on lymphocytes by binding to the multimeric IL-2 receptor (IL-2R) and thereby engaging several intracellular signaling pathways that modulate lymphocyte survival, proliferation, and function (Smith 1988; Theze and others 1996; Nelson and Willerford 1998; Fehniger and others 2002; Kovanen and Leonard 2004; Ma and others 2006; Waldmann 2006, 2014, 2015; Boyman and others 2007; Bodnar and others 2008; D'Cruz and others 2009; Overwijk and Schluns 2009; Rochman and others 2009; Boyman and Sprent 2012; Carrette and Surh 2012; Liao and others 2013; Rosenberg 2014; Sim and Radvanyi 2014; Pulliam and others 2016). The heterotrimeric IL-2R is composed of 3 subunits: IL-2Rα (CD25), IL-2Rβ (CD122), and IL-2Rγ (CD132). IL-2Rβ and IL-2Rγ are essential for intracellular signaling and can form a functional dimeric receptor in the absence of IL-2Rα. Notably, IL-2Rγ is used as part of the receptors for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21, cytokines which can all act on various lymphocyte populations likely partially dictated by differing receptor subunit expression. IL-2, IL-7, and IL-15 have received the most attention for their ability to act on T cells, and in the case of IL-2 and IL-15, also on natural killer (NK) and NK T cells. IL-2 and IL-15 are closely related in that they both signal through the IL-2Rβγ heterodimeric receptor and engage the JAK/STAT, Ras/MAPK, and PI3K/Akt signaling pathways (Nelson and Willerford 1998; Bodnar and others 2008; Boyman and Sprent 2012; Liao and others 2013; Mishra and others 2014; Waldmann 2014). While not necessary for signaling, IL-2 and IL-15 also bind private α chains (IL-2Rα and IL-15Rα), which are structurally related and may have arisen evolutionarily from gene duplication (Giri and others 1995; Tagaya and others 1996). These α chains were initially thought to allow for high affinity receptor binding; however, as will be described below, it is clear that their functional contribution to cytokine signaling is more complicated.

While IL-2 and IL-15 both signal through the shared IL-2Rβγ and mediate similar signaling and functional activity on purified lymphocytes (Willerford and others 1995; Murakami and others 2002; Ring and others 2012; Arneja and others 2014), these cytokines have dramatically different biological activities *in vivo*. This is most apparent in a comparison of knockout mice. IL-2 knockout mice die prematurely as a result of autoimmune disease (Sadlack and others 1993), while IL-15 mice are relatively healthy with reduced numbers of IL-15-dependent cells such as NK cells and CD8 memory T cells (Kennedy and others 2000). These and other differential properties of IL-2 and IL-15 are likely mediated by IL-2 or IL-15 availability and expression of IL-2Rα and IL-15Rα. In particular, T regulatory cells express high and constitutive levels of IL-2Rα, a molecule critical for their survival. Thus, in the absence of IL-2Rα, mature T regulatory cells are absent and mice die prematurely unless IL-2Rα-competent T regulatory cells are provided (Willerford and others 1995; Almeida and others 2002). A patient with a mutated IL-2Rα gene, who had extensive lymphocytic infiltration of tissues accompanied by atrophy and inflammation, suggests that a similar process exists in humans (Sharfe and others 1997).

How IL-2Rα mediates its unique responsiveness to IL-2 has been the subject of much work. IL-2Rα is not known to mediate intracellular signaling and was initially characterized by its ability to promote high affinity binding of IL-2 to the IL-2Rβγ (Smith 1988; Nelson and Willerford 1998; Kovanen and Leonard 2004; Ma and others 2006). Interestingly, IL-2Rα can also promote sustained IL-2 signaling after removal of cytokine, which may be mediated by the ability of IL-2Rα to facilitate cell surface reservoirs of IL-2 and the ability of IL-2Rα to rescue IL-2 from degradation (Bergmann and others 1992; Fallon and others 2000; Rao and others 2004, 2005; Su and others 2015). Thus, in addition to facilitating high affinity binding of IL-2 to its receptor, IL-2Rα allows for temporal responsiveness of IL-2 (Su and others 2015). As activated T cells transiently express high levels of IL-2Rα (Cantrell and Smith 1983; Leonard and others 1985; Gullberg and Smith 1986; Andersson and others 1994; Cousens and others 1995; Obar and others 2010), these IL-2Rα-dependent mechanisms may facilitate the ability of effector T cells to function after being deprived of an IL-2-rich environment or for effector T cells to preserve access to limited amounts of IL-2. In addition to cell-intrinsic IL-2Rα signaling, it has been reported that IL-2Rα may be involved in the trans-presentation of IL-2 to neighboring cells (Eicher and Waldmann 1998; Kronin and others 1998; Fukao and Koyasu 2000; Wuest and others 2011). Soluble IL-2Rα may also play an important role in regulating immune responses (Rubin and others 1985; Baran and others 1988; Gooding and others 1995; Cabrera and others 2010; Hannani and others 2015; Li and others 2016).

Like IL-2Rα, IL-15Rα is unique to its cognate cytokine. IL-15Rα was initially recognized by its ability to facilitate high affinity IL-15 binding (Lodolce and others 1998; Fehniger and Caligiuri 2001; Waldmann and others 2001). However, recent work suggests that the ability of IL-15Rα to present IL-15 either in membrane or soluble form may be more critical (Dubois and others 2002; Burkett and others 2003; Koka and others 2004; Kobayashi and others 2005; Schluns and others 2005; Stonier and others 2008; Castillo and others 2009; Bergamaschi and others 2012). It is unclear whether IL-15 actually exists naturally by itself; rather it may always be associated with either membrane-bound or soluble IL-15Rα (Bergamaschi and others 2012; Castillo and Schluns 2012; Cole and Rubinstein 2012). There are some other notable findings related to IL-15Rα that may be relevant for its ability to function. There is evidence that IL-15Rα might engage membrane-bound IL-15 and mediate reverse signaling (Neely and others 2004; Khawam and others 2009). Unlike IL-2Rα subunit, IL-15Rα may retain some ability to mediate intracellular signaling upon IL-15 engagement, although there is not a consensus on the relevant pathways (Stevens and others 1997; Pereno and others 1999, 2000; Ratthe and Girard 2004; Marra and others 2014). Finally, naturally occurring soluble IL-15Rα has been reported which may impact the activity of IL-15 (Mortier and others 2004; Badoual and others 2008; Bergamaschi and others 2012).

IL-2 Combined with Adoptive Cellular Therapy

While IL-2 has efficacy as a single agent, preclinical work suggesting that coadministration of LAK cells could yield improved responses led to the search for other tumor-reactive lymphocyte populations to combine with IL-2. Yron and others (1980) reported the isolation and expansion of T cells from the tumors of mice using conditioned media containing IL-2. These T cells could kill tumor cells, but did not kill healthy lymphocytes. With the availability of recombinant IL-2, these tumor-infiltrating lymphocytes (TILs) could be more efficiently grown *in vitro*. In 1986, Rosenberg and colleagues reported that upon adoptive transfer in mice, TILs were 50–100-fold more efficacious than LAK cells in mediating antitumor immunity (Rosenberg and others 1986; Muul and others 1987). Importantly, in these experiments, the activity of TILs was enhanced by the administration of IL-2. In tandem with their characterization in mice, it was found that TILs could be generated from many types of human tumors (Kurnick and others 1986; Topalian and others 1987; Rosenberg 1992). In 1987, Kurnick and colleagues reported the administration of TIL to human patients with the treatment of 7 patients with metastatic adenocarcinoma of the lung (Kradin and others 1987). While there were no objective responses of at least 50% total reduction in tumor volume, the authors noted that 5 of 7 patients had some reduction in tumor volume. During the next 2 years, Kurnick and colleagues published 2 more studies in human patients using TIL with the addition of recombinant IL-2 (Kradin and others 1988, 1989). The authors observed partial (objective) responses in 3 of 13 melanoma patients and 2 of 7 renal cell carcinoma patients (Kradin and others 1988, 1989). During this same time, Rosenberg and colleagues also reported clinical trials using TIL with the addition of IL-2 administration (Rosenberg and others 1988; Topalian and others 1988). Based on mouse studies showing that preconditioning with cyclophosphamide was important for TIL efficacy (Rosenberg and others 1986), Rosenberg and colleagues administered cyclophosphamide to patients before TIL infusion. With the combination of cyclophosphamide, TIL, and high-dose IL-2, Rosenberg and colleagues achieved objective responses in 11 of 20 metastatic melanoma patients (Rosenberg and others 1988). Notably, 2 objective responses were observed among 5 patients in whom IL-2 therapy alone had failed to yield a response. Although there were limited numbers of patients and varying treatment protocols, there was great excitement that TIL therapy administered with IL-2 appeared to allow response rates much higher than that observed with IL-2 therapy alone. Importantly, and indicative of TIL's ability to mediate direct antitumor immunity, Griffith and others (1989) reported that indium-111 labeled TIL preferentially localized to tumor versus normal skin.

Several other reports warrant mention in better understanding TIL therapy and the relationship to IL-2. First, to more accurately define the response rate in a larger cohort of patients, Rosenberg and colleagues reported results of 86 patients with metastatic melanoma treated with TIL and IL-2 from May 1987 to December 1992 (Rosenberg and others 1994). The objective response rate from TIL therapy with IL-2 administration for these patients was 34%, a response rate much higher than what might have been expected with IL-2 alone. As part of the study, 59 of 86 patients received a single dose of cyclophosphamide (25 mg/kg) before TIL infusion. The response rate in patients without cyclophosphamide (31%) was not statistically different than patients with cyclophosphamide (35%) (Rosenberg and others 1994).

While a single injection of cyclophosphamide did not appear to significantly improve response rates of TIL therapy with IL-2, extensive studies in animals did suggest that lymphodepletion (using total body irradiation or chemotherapy) before adoptive cellular therapy would greatly improve donor lymphocyte persistence and antitumor efficacy (Glynn and others 1969; Berendt and North 1980; North 1982; Greenberg and others 1985, 1988; Rosenberg and others 1986; Muranski and others 2006; Paulos and others 2007; Wrzesinski and others 2010). Multiple mechanisms have been reported to mediate these effects, including the reduction of tumor burden, the destruction of suppressive cells, increased antigen presenting cells, and the release of lipopolysaccharide (LPS) from host microflora (Hill and others 1997; Zhang and others 2002; Brown and others 2004; Klebanoff and others 2005; Gattinoni and others 2006; Paulos and others 2007; Salem and others 2009; Yao and others 2012). Perhaps most relevant is the destruction of host lymphocytes which consume T cell growth factors such as IL-2, IL-7, or IL-15 (Schluns and others 2000; Tan and others 2001, 2002; Goldrath and others 2002; Gattinoni and others 2005; Johnson and others 2015; Martin and others 2017). The absence of host lymphocytes may also improve the availability of recombinant IL-2 for donor T cells. Furthermore, as IL-7 and IL-15 are produced by radiation-resistant cells, lymphodepletion leads to dramatically elevated IL-7 and IL-15 in mice and humans (Bolotin and others 1999; Fry and others 2001; Napolitano and others 2001; Miller and others 2005; Dudley and others 2008; Guimond and others 2009; Bergamaschi and others 2012). A demonstration of clinical relevance of lymphodepletion was reported in 2002 in patients with metastatic melanoma treated with TIL therapy and IL-2. In this trial, a much harsher conditioning regimen was provided with 2 days of cyclophosphamide (60 mg/kg) and 5 days of fludarabine (25 mg/m^2) (Dudley and others 2002). This enhanced nonmyeloablative lymphodepletion conditioning regimen given with TIL and IL-2 resulted in objective responses in 6 of 13 patients. Notably, in this study TIL persisted at a greater level than in previous studies (Dudley and others 2002). Although the enhanced lymphodepletion regimen was likely critical, it is relevant that the T cell culture conditions in this study were different than earlier TIL studies in that a new rapid expansion protocol with both irradiated feeder cells and soluble anti-CD3 mAb was used to expand the cells immediately before infusion (Dudley and others 2002).

The success of lymphodepletion with cyclophosphamide and fludarabine led to additional interest in whether greater lymphodepletion might further improve response rates. Studies in mice suggested that the addition of total body irradiation to standard lymphodepletion would improve outcomes (Muranski and others 2006; Paulos and others 2007; Wrzesinski and others 2010). This rationale provided the framework for evaluating whether the addition of total body irradiation to standard cyclophosphamide and fludarabine would lead to improved clinical response of TIL therapy with IL-2. In initial studies, Rosenberg and colleagues observed higher response rates with the addition of 2 Gy ($n=25$) or 12 Gy ($n=25$) total body irradiation compared with the standard lymphodepletion nonmyeloablative conditioning regimen ($n=43$) (Dudley and others 2008; Rosenberg and others 2011). However, another study reported no benefit of the addition of 6 Gy ($n=25$) total body irradiation versus standard cyclophosphamide and fludarabine ($n=33$) (Dudley and others 2010). To evaluate the value of total body irradiation, Rosenberg and colleagues performed a randomized study with ($n=50$) or without ($n=51$) 12 Gy total body irradiation in addition to standard cyclophosphamide and fludarabine (Goff and others 2016). In both groups, 24% of patients experienced complete responses, and there were no significant differences in overall survival (Goff and others 2016). Contrary to expectations, enhanced lymphodepletion did not improve the response rate of TIL and IL-2. These results suggest that there may be a threshold of lymphodepletion that is adequate for optimal antitumor responses. It is unclear if or how providing IL-2 support after administration of TIL may alter the optimal level of lymphodepletion.

While the addition of total body irradiation is unnecessary for the efficacy of TIL therapy, the ability of an enhanced, nonmyeloablative lymphodepletion regimen to mediate effective responses when given with TIL and IL-2 has now been reported by multiple groups (Pilon-Thomas and others 2012; Radvanyi and others 2012; Besser and others 2013). However, due to the difficulties in conducting these studies, the changing patient population, and evolving protocol designs, the optimal level of lymphodepletion and subsequent IL-2 support for patients receiving TIL therapy are yet to be determined.

While TIL has received much attention, other endogenous tumor-reactive T cell populations have been isolated, expanded, and used for cancer therapy (Yee and others 2002; Wallen and others 2009; Verdegaal and others 2011, 2016; Chapuis and others 2012, 2013; Yee 2014). In a striking example demonstrating the benefit of IL-2, Yee and others (2002) treated metastatic melanoma patients with multiple infusions of MART-1- and GP100-reactive CD8$^+$ T cell clones in which patients received no lymphodepleting chemotherapy. After the first infusion, patients received no IL-2 therapy, but after subsequent infusions, patients received increasing amounts of low-dose IL-2 given subcutaneously (0.25, 0.5, and 1.0×10^6 U/m^2 twice daily for 14 days) (Yee and others 2002). The authors found that T cells persisted much better when IL-2 was administered after adoptive transfer; however, most donor T cells failed to persist beyond 21 days in the blood. There were no objective responses, although 8 of 10 patients had minor, mixed, or stable responses for up to 21 months. It is relevant in this study that the T cells expressed IL-2Rα, which may have facilitated their responsiveness to low-dose IL-2. In a follow-up study in 11 patients with metastatic melanoma, Chapuis and others (2012) added cyclophosphamide (4 g/m^2) before adoptive transfer of tumor-reactive T cell clones. Three patients received high-dose IL-2; however, this cohort was discontinued due to toxicity. Eight patients received low-dose IL-2, which was ''well tolerated and safe'' (Chapuis and others 2012). In this study, 4 of 11 patients had T cell persistence beyond 42 days. Furthermore, 1 patient had a complete response, and 5 had stable disease. These results further suggest that the appropriate balance between lymphodepletion and IL-2 therapy can lead to optimal T cell persistence and clinical responses.

IL-2 Combined with Genetically Modified T Cells

A significant advance in adoptive cellular therapy (ACT) was the development of methods to genetically engineer tumor-reactivity using the transfer of T cell receptor (TCR) or chimeric antigen receptor (CAR) genes (Gross and others

1989; Cole and others 1995; Kaplan and others 2003; Restifo and others 2012; Kochenderfer and Rosenberg 2013; Barrett and others 2014; Jensen and Riddell 2014; Kenderian and others 2014; Stromnes and others 2014; Nelson and Paulos 2015; Debets and others 2016; Sharma and Kranz 2016; Spear and others 2016; Turtle and others 2016; Lim and June 2017; Wang and Wang 2017). These approaches offer the possibility of generating tumor-reactive cells in patients who do not already possess such cells or where they cannot be isolated. Thus, for example, in metastatic melanoma it is estimated that only ~27% to 45% of patients are able to receive TIL therapy due to factors such as inability to isolate tumor, inability to expand TIL, or patient disease progression during TIL preparation (Prieto and others 2010; Rosenberg and others 2011). The therapeutic utility of TCR- and CAR-modified T cells given with or without IL-2 is supported by studies in mice (Kessels and others 2001; Brentjens and others 2003; Chamoto and others 2004; Xue and others 2005; Chinnasamy and others 2010; Kochenderfer and others 2010b).

The successful translation of these efforts in humans was first reported in 2006 by Rosenberg and colleagues who adoptively transferred TCR-modified T cells into patients with metastatic melanoma (Morgan and others 2006). In this study, patients received nonmyeloablative chemotherapy, T cells genetically modified with a MART-1-reactive TCR, and high-dose IL-2. There were objective responses in 2 of 15 patients. Notably, these 2 patients had failed previous IL-2 therapy and also had remarkable persistence of their donor lymphocytes (Morgan and others 2006). Since this first experience, there have been multiple clinical trials using TCR-modified T cells, including TCRs reactive against CEA, MART-1, GP100, NY-ESO-1, MAGE-A3, and MAGE-A4 (Johnson and others 2009; Parkhurst and others 2011; Robbins and others 2011, 2015; Morgan and others 2013; Chodon and others 2014; Kageyama and others 2015; Rapoport and others 2015). In most of these studies, high-dose IL-2 was provided immediately after adoptive T cell transfer. Two studies of NY-ESO-1-reactive TCR-modified T cells are notable. Steven Rosenberg and colleagues used NY-ESO-1-reactive TCR-modified T cells in combination with lymphodepletion and high-dose IL-2 to successfully induce objective responses in 22 of 38 patients with either metastatic melanoma or synovial cell carcinoma (Robbins and others 2011, 2015). June and colleagues also used NY-ESO-1-reactive TCR-modified T cells to treat multiple myeloma and observed clinical responses in 16 of 20 patients, although without providing IL-2 (Rapoport and others 2015). As there were many differences between these studies, including the type of cancer, the methodology by which the T cells were expanded, and method of lymphodepletion, the value of IL-2 in these protocols is not clear.

While TCR-modified T cells show great promise in the treatment of solid tumors, the use of CAR-modified T cells has shown spectacular success in patients with B cell neoplasms. These recent successes followed a number of early clinical trials using CAR-modified T cells that did not result in clinical benefit (McGuinness and others 1999; Kershaw and others 2006; Lamers and others 2006; June and others 2014). In 2010 however, initial success was demonstrated by Kochenderfer and others (2010a) who used T cells modified with CD19-reactive CAR in combination with IL-2 to induce a response in a patient with advanced follicular lymphoma. A follow-up study by the same group in 2012 showed objective responses in 6 of 8 patients with advanced, progressive B cell malignancies that had failed other therapies (Kochenderfer and others 2012). These patients all received nonmyeloablative chemotherapy with cyclophosphamide and fludarabine followed by CAR-modified T cells and recombinant IL-2. In 2011, June and colleagues reported another major advance using another CD19-reactive CAR (Kalos and others 2011). In this case, the intracellular signaling domain of the CAR was modified with a 4-1BB signaling domain, and a modified, shorter T cell culture was used. Three patients with advance chronic lymphoid leukemia were treated with nonmyeloablative chemotherapy and CAR-modified T cells, but with no IL-2. All 3 patients had clinical responses, including 2 complete responses (Kalos and others 2011). June and colleagues, as well as other groups, have now extensively reported results demonstrating incredible efficacy of CD19-reactive CAR T cells in patients with a variety of B cell malignancies (Brentjens and others 2013; Grupp and others 2013; Maude and others 2014; Garfall and others 2015; Kochenderfer and others 2015; Lee and others 2015; Brudno and others 2016; Kebriaei and others 2016; Locke and others 2017). It is notable that for the most part, these studies have not used exogenous IL-2. Again, as was the case with other T cell therapies, the potential benefit and importance of IL-2 therapy are not clear, as between the various studies, there are differences, including cell culture conditions, lymphodepletion, and the CAR signaling domains. In the case of CD19-reactive CAR T cells, it may also be relevant that a large population of $CD19^+$ nontumor cells might provide stimulation in such a manner that cytokine therapy is not necessary. However, a study by Kochenderfer and others (2017) reported an association between clinical response and elevated endogenous IL-15 (but not IL-2) in the serum, suggesting that IL-2 or IL-15-based therapy could have value as part of CAR therapy.

Alternatives to IL-2 Therapy

While administration of IL-2 is associated with remarkable clinical responses in certain patients, dose limiting toxicities make the widespread administration of this therapy infeasible. Side effects from high-dose IL-2 can be severe and include fever, chills, hypotension, tachycardia, oliguria, nausea, vomiting, diarrhea, capillary leak syndrome, renal failure, and thrombocytopenia requiring the use of blood pressure monitoring, volume replacements, and blood pressure support if needed. These side effects, however, are manageable when therapy is administered at experienced centers (Lotze and others 1986b; Rosenstein and others 1986; Kammula and others 1998; Dutcher and others 2001; Schwartzentruber 2001).

In addition to toxicity, IL-2 administration for cancer therapy carries the concern for expansion of T regulatory cells. T regulatory cells are especially responsive to IL-2 because they constitutively express high levels of the IL-2Rα subunit, necessary for high affinity IL-2 binding (Nishikawa and Sakaguchi 2014; Shevach and Thornton 2014; Yuan and others 2014; Waldmann 2015). The importance of IL-2 and T regulatory cells is particularly evident by the phenotypes of IL-2, IL-2Rα, and IL-2Rβ knockout mice, which all develop fatal autoimmunity (Sadlack and others 1993, 1995; Suzuki and others 1995;

Willerford and others 1995; Yu and others 2003). Thus, while recombinant IL-2 can potently augment immune responses, it paradoxically plays a critical role in expanding a cell population that can shut down immune responses. The clinical relevance of this is suggested in patients treated with recombinant IL-2, where increased frequencies of $FOXP3^+$ T regulatory cells have been reported (Zhang and others 2005; Ahmadzadeh 2006; Yao and others 2012). The ability of IL-2 to induce regulatory cells has been exploited to treat autoimmune disease. Thus, low doses of IL-2 have been given with clinical success to treat patients with chronic graft-versus-host disease, hepatitis C virus-induced vasculitis, and systemic lupus erythematosus (Koreth and others 2011; Saadoun and others 2011; Matsuoka and others 2013; He and others 2016). In addition to inducing T regulatory-mediated suppressive pathways (Matsuoka and others 2013; He and others 2016), low-dose IL-2 has also been shown in patients to induce the expansion of NK cell populations that may have antitumor potential (Caligiuri and others 1993). Thus, the interplay of IL-2-induced expansion of effector cells and regulatory cells is quite complicated.

One method to improve the utilization of high-dose IL-2 therapy would be to identify biomarkers to predict patients likely to respond. However, while there has been work to identify such biomarkers (Royal and others 1996; Bui and others 2003; Leibovich and others 2003; Atkins and others 2005; Upton and others 2005; Dudek and others 2010; Foureau and others 2014; Sim and others 2014; Kostner and others 2015; McDermott and others 2015a; Saraceni and others 2015; Chow and others 2016; Diller and others 2016; Kuzman and others 2017), there are no biomarkers that have been widely adopted to predict patients likely to respond. Newer methods and approaches for biomarkers have shown great promise in checkpoint therapy (Gibney and others 2016; Topalian and others 2016; Maleki Vareki and others 2017; Nishino and others 2017), but these methods have had limited evaluation in the context of IL-2 therapy. Notably, McDermott and others (2015a) reported that evidence in renal cell carcinoma that elevated PD-L1 expression in pretreatment tumors was favorably associated with clinical response. While being able to select patients likely to respond would be of value, there has been much effort to identify novel cytokine therapeutics with improved efficacy and reduced toxicities.

IL-15

The discovery in 1994 of IL-15 (Burton and others 1994; Grabstein and others 1994), which like IL-2 signals through the IL-2Rβγ subunits, raised the possibility that this novel cytokine might provide a therapeutic alternative to IL-2. Studies in mice suggested that toxicity at therapeutic doses associated with IL-15 might be more favorable than IL-2 (Munger and others 1995; Katsanis and others 1996; Kobayashi and others 2000). Given the similarities and potential advantages relative to IL-2, IL-15 was evaluated preclinically and showed efficacy in multiple models, including induction of antitumor immunity (Munger and others 1995; Evans and others 1997; Cao and others 1998; Di Carlo and others 2000; Rubinstein and others 2002; Kishida and others 2003; Oh and others 2003; Klebanoff and others 2004; Lasek and others 2004; Roychowdhury and others 2004; Melchionda and others 2005; Ugen and others 2006; Basak and others 2008; Habibi and others 2009; Liu and others 2013). Notably, recombinant IL-15 enhances the efficacy of adoptively transferred tumor-reactive T cells given concomitantly with vaccination in mice bearing established subcutaneous melanoma tumors (Klebanoff and others 2004). Given a variety of preclinical results, enthusiasm for IL-15 led to it being ranked first by the 2007 NCI immunotherapy agent workshop as the experimental agent with highest potential for treating cancer (Cheever 2008). In 2015, Waldmann and colleagues reported that they could safely administer IL-15 to patients and induce biological activity on NK cells and $CD8^+$ memory T cells (Conlon and others 2015). Although there were no objective responses, there was clearance of lung lesions in 2 patients with metastatic melanoma (Conlon and others 2015). Waldmann and colleagues have recently reported a second cohort of patients treated with recombinant IL-15 and provided a detailed analysis of the response of NK cells to treatment (Dubois and others 2017).

While IL-15 has shown great promise as an antitumor agent, in 2006 it was found that the biological activity of IL-15 could be further improved by preassociation with its soluble receptor, IL-15Rα (Mortier and others 2006; Rubinstein and others 2006; Stoklasek and others 2006; Bergamaschi and others 2008; Dubois and others 2008), thereby creating IL-15/IL-15Rα complexes. Interestingly, *in vitro* association of IL-15 with either a monomeric or dimeric sIL-15Rα (fused to an Fc) led to greatly improved activity (Rubinstein and others 2006). These results suggest that when bound to IL-15Rα, IL-15 might undergo a conformational change into a superagonist (Rubinstein and others 2006). Structural evidence in support of this was subsequently reported by Garcia and colleagues (Ring and others 2012). While the activity of these IL-15/sIL-15Rα complexes was notable *in vitro*, upon infusion, IL-15/sIL-15Rα complexes mediated more than 50-fold greater activity than free IL-15 (Rubinstein and others 2006; Stoklasek and others 2006). As sIL-15Ra-Fc only improved IL-15 activity about 7-fold *in vitro* (Rubinstein and others 2006), these data suggest that there are additional mechanisms leading to improved biological activity *in vivo*. Potential mechanisms accounting for the improved activity *in vivo* include the ability of sIL-15Ra-Fc to act as a carrier protein, to redirect the localization of IL-15, and to protect IL-15 from proteolytic degradation.

The increased biological activity of IL-15/sIL-15Rα-Fc complexes *in vivo* is apparent in multiple readouts. IL-15/sIL-15Rα complexes induce the potent expansion of cell types important to antitumor immunity (including $CD8^+$ memory T cells, NK cells, and NK T cells) and mediate potent antitumor immunity in mouse models (Rubinstein and others 2006; Stoklasek and others 2006; Bergamaschi and others 2008; Dubois and others 2008; Epardaud and others 2008; Bessard and others 2009; Desbois and others 2016). Following infection in mice, IL-15/sIL-15Rα-Fc complexes were also able to effectively augment the number of responding antigen-specific $CD8^+$ T cells demonstrating the potential of this reagent to have efficacy with vaccination approaches (Epardaud and others 2008). In the interest of clinical translation, several groups have generated IL-15/sIL-15Rα complexes with or without inclusion of an Fc (Bouchaud and others 2008; Rowley and others 2009; Han and others 2011; Stone and others 2012; Tosic and others

2014). Notably, Wong and colleagues generated IL-15/IL-15Rα complexes with an amino acid mutation that further improved biological activity (Han and others 2011). This molecule has shown potent efficacy in augmenting antitumor responses in murine tumor models, and also, in inducing the expansion of lymphocytes in cynomolgus monkeys (Xu and others 2013; Gomes-Giacoia and others 2014; Rhode and others 2016). This molecule, which has been designated ALT-803, is currently in clinical testing. In addition to ALT-803 manufactured by Altor Bioscience, other IL-15/IL-15Ra complexes are in development by Novartis (Admune) and Cytune Pharma (Desbois and others 2016; Thaysen-Andersen and others 2016).

IL-7

IL-7 has been reviewed in detail elsewhere (Hofmeister and others 1999; Fry and Mackall 2002; Jiang and others 2005; Ma and others 2006; Mazzucchelli and Durum 2007; Overwijk and Schluns 2009; Mackall and others 2011; Carrette and Surh 2012; Lin and others 2017). IL-7 has many similarities with IL-2 and IL-15, including utilization of the shared IL-2Rγ subunit. IL-7 and its second receptor subunit, IL-7Rα, were cloned in the late 1980s (Namen and others 1988; Goodwin and others 1989, 1990). While IL-7Rα does not interact with any other IL-2Rγ-chain cytokine members, in conjunction with the thymic stromal lymphopoietin receptor (TSLPR), IL-7Rα mediates signaling and biological activity of TSLP in a wide range of immune cells (Levin and others 1999; Pandey and others 2000; Park and others 2000; Roan and others 2012; Lo Kuan and Ziegler 2014). The IL-7 receptor, IL-7Rα/IL-2Rγ, is expressed on both developing and mature B cells and T cells. Mice deficient in IL-7, IL-7Rα, or IL-2Rγ have a severe combined immunodeficiency (SCID) phenotype consistent with the critical role in these cytokines and receptors in lymphocyte development and survival (Peschon and others 1994; Cao and others 1995; von Freeden-Jeffry and others 1995). The lymphopenia of the IL-7Rα KO mouse is slightly more severe than the IL-7 KO mouse, suggesting that TSLP may play a role in supporting lymphocyte development and survival (Pandey and others 2000). Studies using IL-7 transgenic mice and administration of recombinant IL-7 into mice show that exogenous IL-7 can greatly augment the numbers of both T cells and B cells, although both mature and immature B cells are expanded (Morrissey and others 1991; Samaridis and others 1991; Damia and others 1992; Komschlies and others 1994; Fisher and others 1995; Mertsching and others 1995; Valenzona and others 1996; Melchionda and others 2005; Nanjappa and others 2008). In preclinical models, IL-7 administration can promote immune responses against tumor and infectious disease (Nanjappa and others 2008, 2011; Andersson and others 2009; Cui and others 2009; Pellegrini and others 2011; Tang and others 2014; Ruan and others 2016). It is noteworthy that surface expression of IL-7Rα is high on naive and memory T cells, but reduced upon T cell activation, suggesting that effector T cells may have reduced ability to respond to IL-7 (Foxwell and others 1992; Schluns and others 2000; Goldrath and others 2002; Xue and others 2002; Kaech and others 2003; Klonowski and others 2006). However, depending on the method of T cell activation, there may be sufficient surface IL-7Rα on effector T cells for IL-7 responsiveness (Johnson and others 2015).

The first human trial for the evaluation of IL-7 was reported in 2006 when Rosenberg and others (2006) demonstrated that IL-7 administration to cancer patients could enhance $CD8^+$ and $CD4^+$ T cell counts, with reduced frequencies of T regulatory cells, but with no objective responses. A number of other clinical studies have also evaluated IL-7 in human patients, including in cancer and HIV infection (Sportes and others 2008, 2010; Levy and others 2009, 2012; Sereti and others 2009; Perales and others 2012; Alstadhaug and others 2014; Gasnault and others 2014; Tredan and others 2015; Sheikh and others 2016; Thiebaut and others 2016). It is notable that the pre-B cell expansion observed in murine models was not apparent in humans, suggesting a critical difference between mouse and humans (Sportes and others 2010). Furthermore, unlike IL-2 therapy, IL-7 therapy does not lead to the expansion of $CD4^+CD25^+$ T regulatory cells (Rosenberg and others 2006; Sereti and others 2009; Sportes and others 2010).

Novel IL-2 based therapies

The design of mutant IL-2 molecules provides another option for improving the biological activity of IL-2. Several groups have designed IL-2 mutants that have reduced binding to IL-2Rα and in some cases have enhanced binding to IL-2Rβγ (Heaton and others 1993; Levin and others 2012; Carmenate and others 2013). These molecules have shown improved antitumor efficacy and reduced toxicity in animal models. An alternative approach has been the generation of IL-2 mutants with enhanced ability to bind IL-2Rαβγ relative to IL-2Rβγ. Shanafelt and others (2000) designed an IL-2 mutant with reduced IL-2Rβγ binding with the goal of minimizing toxicity mediated by $IL\text{-}2R\beta\gamma^+$ NK cells. This molecule, designated BAY 50-4798, was tested as a single agent in cancer patients. While able to induce some clinical responses in cancer patients, there were not obvious advantages compared with conventional IL-2 with the treatment protocol (Margolin and others 2007). In a related approach, other groups have designed mutant IL-2 molecules with improved binding of IL-2 to IL-2Rα. Fallon and others (2000) reported an IL-2 analog that may undergo increased endosomal recycling due to an alteration in the pH sensitivity between IL-2 and IL-2Rα. In separate studies, Rao and others also generated IL-2 mutants with improved affinity for IL-2Rα (Rao and others 2003, 2005). Unlike wild-type IL-2, these mutants could persist on the cell surface and mediate durable cell signaling as has been reported for IL-15 (Dubois and others 2002). Whether these mutant IL-2 molecules have clinical efficacy, and under what circumstances, remains to be determined.

While there has been much effort to augment or tailor IL-2 signaling, there are also mutants of IL-2 designed to inhibit signaling (Liu and others 2009; Mitra and others 2015). For example, Liu and others (2009) designed an IL-2 antagonist by selecting for high affinity binding to IL-2Rα and loss of binding to IL-2Rβγ. These molecules may selectively block high affinity IL-2 signaling and, for example, could suppress T regulatory responses. While mutant IL-2 molecules have promise, it is also worth mention that Tsytsikov and others (1996) reported natural variants of IL-2, generated by alternative splicing, that may competitively inhibit full length IL-2.

In addition to modifying the specificity of IL-2, other approaches seek to improve the half-life and biological activity of IL-2. Pegylation of recombinant molecules can improve half-life and biological activity (Pasut and Veronese 2009;

Milla and others 2012; Turecek and others 2016), and pegylated IL-2 (PEG-IL-2) molecules have been generated with improved biological activity, half-life, and antitumor activity versus nonpegylated IL-2 (Katre and others 1987; Knauf and others 1988; Zimmerman and others 1989; Katre 1990; Yang and others 1991; Charych and others 2016). Administration of PEG-IL-2 to patients with metastatic melanoma and renal cell carcinoma was associated with objective responses (Meyers and others 1991; Yang and others 1995). Another benefit of this approach is that the pegylation process may alter the IL-2 to redirect its target cell specificity. NKTR-214 is IL-2 that has been pegylated in a way to reduce or mask its ability to engage to IL-2Rα, thereby making it more like IL-15 (Charych and others 2016). NKTR-214, which is produced by Nektar, is in clinical testing. Other methods for improving the half-life of IL-2 include the generation of fusion proteins, including the linkage of IL-2 with the Fc region of an antibody or albumin (Zheng and others 1999; Yao and others 2004; Melder and others 2005).

IL-2 therapy using antibody/cytokine complexes

Another method to increase the biological activity of IL-2 is by preassociation with anti-IL-2 mAb, to generate IL-2/mAb complexes, before infusion. IL-2/mAb complexes were first reported in 1993 and showed greatly enhanced antitumor efficacy versus free IL-2 (Sato and others 1993; Courtney and others 1994). The enhancement of activity was associated with improved IL-2 persistence *in vivo*. There are a number of potential enhancing mechanisms that may be responsible for this improved activity, including improved half-life, protection from degradation, and altered localization. Interestingly, despite these early studies demonstrating that antibodies could enhance the biological activity of IL-2, the administration of anticytokine monoclonal antibodies to reduce IL-2 responses was routine. In fact, it was thought that administration of anti-IL-2 mAb would block IL-2 and thus reduce T regulatory cell activity resulting in improved proliferation of $CD8^+$ memory-phenotype T cells. However, in 2006, Boyman and others (2006) demonstrated that instead of blocking IL-2, anti-IL-2 mAb promoted the biological activity of endogenous IL-2, thus directly stimulating $CD8^+$ memory-phenotype T cells. Furthermore, injection of preformed IL-2/mAb complexes exhibited potent biological activity on $CD8^+$ memory-phenotype T cells and NK cells.

Another important property of IL-2/mAb complexes is that target cell specificity can be altered compared with native IL-2 (Boyman and others 2006). Thus, depending on the choice of anti-IL-2 mAb, IL-2 can be redirected either in favor of IL-2Rα^{hi} T cells or independent of IL-2Rα expression. The ability to redirect IL-2 target cell specificity may relate to the ability of anti-IL-2 mAb to block the IL-2 interaction with certain cytokine receptor subunits or may conformationally stabilize certain interactions (Spangler and others 2015).

IL-2/mAb complexes have now shown efficacy in augmenting immune responses in a wide range of preclinical models, including antitumor immunity (Jin and others 2008; Mostbock and others 2008; Wilson and others 2008; Molloy and others 2009; Tomala and others 2009; Webster and others 2009; Hamilton and others 2010; Krieg and others 2010; Liu and others 2010; Smith and others 2011; Lee and others 2012; Kim and others 2013, 2015). In addition to antibody cytokine complexes generated with IL-2, it is relevant that cytokine complexes have also been reported with IL-4, IL-7, and IL-15 with potent biological activity, including on lymphocytes (Finkelman and others 1993; Boyman and others 2008; Phelan and others 2008; Rubinstein and others 2008; Morris and others 2009; Finch and others 2011).

Combination Therapies with IL-2

While IL-2 has shown remarkable efficacy, most patients do not achieve a clinical response. If IL-2 or related cytokines are to benefit a broader group of cancer patients, combinational therapies will likely be necessary. One advantage of IL-2-type therapies is the ability to integrate into almost any other form of immune- or nonimmune therapy. Thus, in any situation where T cells or NK cells participate in mediating immune responses, IL-2 therapy could mediate improved responses. Two therapies in particular warrant discussion and may benefit from the addition of IL-2 therapy: antibody-based therapies targeting tumor cells and immune-checkpoint therapies.

Antibody therapies can target tumor associated antigens and initiate antibody dependent cell-mediated cytotoxicity or complement-mediated lysis. IL-2 or IL-15-based therapies can expand and activate Fc^+ lymphocytes such as NK cells that may directly improve the efficacy of such antibody-mediated therapeutics. A number of preclinical studies show synergy of IL-2 or IL-15 with such antibody-based therapies, and furthermore, depletion of NK cells can abrogate this effect (Eisenbeis and others 2004; Abes and others 2010; Tzeng and others 2015; Zhu and others 2015; Rosario and others 2016). These efforts have led to a number of clinical studies combining IL-2 therapy with rituximab (anti-CD20 mAb) or herceptin (anti-Her2/neu mAb) (Eisenbeis and others 2004; Khan and others 2006; Mani and others 2009; Poire and others 2010). An ongoing clinical trial involves combining ALT-803 (IL-15/IL-15Ra complexes) with rituximab for the treatment of non-Hodgkin's lymphoma (NCT02384954). This combinatorial approach may also have promise in the treatment of infectious diseases where antibodies are currently being evaluated.

Immune checkpoint therapy has shown efficacy in a growing number of cancers, including metastatic melanoma and renal cell carcinoma (Hodi and others 2010; Topalian and others 2012; Hamid and others 2013; Wolchok and others 2013; McDermott and others 2015b; Motzer and others 2015; Schadendorf and others 2015; Sharma and Allison 2015), but likely act in mechanistically distinct ways from IL-2-mediated therapy, thereby suggesting value for combinatorial therapy. Most simply, immune checkpoint therapies may overcome negative regulatory pathways, while cytokine therapies may expand and activate newly available tumor-specific T cell populations. In support of the potential synergy of these approaches, preclinical studies using tumor models and chronic viral infection have shown that IL-2- and IL-15-based therapies synergize with both anti-PD-1 and anti-CTLA-4 mAbs (Yu and others 2010; John and others 2013; West and others 2013; Desbois and others 2016; Mathios and others 2016), and other preclinical mechanistic studies also support the use of these combinations (Shi and others 2016; Asano and others 2017). In humans, there has been only 1 published report of a clinical trial directly combining immune checkpoint therapy with

either IL-2 or IL-15. Rosenberg and others described treating 36 patients with metastatic melanoma with anti-CTLA-4 mAb (ipilimumab) and high-dose IL-2. The authors reported 3 (8%) complete responses in the initial analysis and 6 (17%) complete responses in the longer follow-up (Maker and others 2005; Prieto and others 2012). Although only a small number of patients were enrolled in this study, these results provide clinical support for combining checkpoint therapy with common γ-chain agonist cytokines. Notably, a follow-up study of high-dose IL-2 and ipilimumab is ongoing (NCT02203604). There are several other relevant trials ongoing, including the combination of IL-15/IL-15Rα complexes (ALT-803, NCT02523469), pegylated IL-2 (NKTR-214, NCT02983045, and NCT03138889), and high- and low-dose IL-2 (NCT02964078, NCT02989714, and NCT03111901) with anti-PD-1 mAbs (nivolumab and pembrolizumab) and anti-PD-L1 mAb (atezolizumab). While not concomitant therapy, also of interest is a case report of patient with metastatic renal cell carcinoma who did not respond to anti-PD-1 mAb, but did achieve a near complete response to subsequent IL-2 therapy (Brayer and Fishman 2014).

Conclusion

Immunotherapy is now commonplace for multiple malignancies, and in many ways, the use of IL-2 pioneered the introduction of this therapeutic modality into oncologic practice. While the use of high-dose IL-2 has remained a therapy only available at specialized centers, this therapy has given proof of principle for an alternate and potentially curative paradigm. While much has been learned about the IL-2 and related cytokines since their initial discovery, this area of research remains intensely active with multiple pharmaceutical companies aggressively pursuing clinical investigation of novel and safer IL-2 related reagents. Future directions will likely include combinatorial strategies that take advantage of the broad activity mediated by IL-2 and related cytokine therapeutics.

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