Quantitative systems pharmacology modeling of biotherapeutics in oncology

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Section V.
Summary, discussion, and conclusion

Chapter 8

Summary, discussion, and conclusion

8.1 Mechanistic modeling in oncology research

The high cost and attrition of the drug development process is a fundamental challenge in biomedical research and requires novel approaches to improve efficiency and effectiveness [1]. This is particularly true in oncology drug development, which has the lowest success rate of all therapeutic areas [2]. Cancer treatment has been revolutionized with the advent of immune-oncology therapies; however, the biology is complex and difficult to translate and currently only a minority of patients are benefiting. Simultaneously, there has been rapid innovation in the field of protein engineering which has led to an explosion in the number of biological modalities being explored [3], including an increasing number of cell therapies [4]. Combination approaches are actively being pursued as a means of treating the heterogeneity of the disease across and within patients and reducing the risk of relapse to therapy. However, combination therapy is being approached as a 'trial and error process' in patients. A recent report showed that there were approximately 4000 immune-oncology drugs in development, and greater than 5000 clinical trials [5]. A more systematic process is required to enable more patients to benefit and to reduce clinical failures.

Mathematical modeling-based approaches have been shown to improve productivity in drug development and enhance decision making. Indeed, a recent publication by the FDA states that quantitative pharmacology modeling and simulation are seen as critical to accelerating drug development and assisting in regulatory decisions [1]. In the last two decades modeling and simulation has evolved from a tool primarily used in later stage clinical drug development, to playing a significant role in early clinical development (Phase 1 studies) and most recently in preclinical drug discovery and development [6]. As a result, the types of modeling and simulation approaches have evolved to support translational predictions across systems and species. Empirical PK/PD models have proved very useful in preclinical and clinical development to maximize information obtained from in vivo experiments, while minimizing resource utilization. These models are easy to develop and use, portable and good at extrapolating within a limited field of vision, across different doses and sub-populations [7]. However, they are limited in their ability to predict efficacy and safety across different targets and biomarkers. As a result, more mechanistic modeling and simulation is now being used to understand specifics of the pharmacology and mechanism of action of drugs to translate from in vitro experiments, to preclinical species and ultimately to human. These models are more data integrative, linking the exposure of drugs (or combination of drugs) and the modulation of pharmacological targets, physiological pathways and disease systems and can be used to develop a unified understanding of the data collected at different stages of drug discovery and development, and as such can provide a quantitative framework for drug research [6]. These mechanistic models have been termed 'quantitative systems pharmacology' or QSP models [7]. A key feature of these models is their explicit distinction between 'drug' and 'system' parameters. System specific parameters typically include organ/tissue blood flow rates, receptor expression, internalization rates and turnover rates, cell lifespans, and homoeostatic feedback mechanisms. Ideally, these parameters should be available from the literature or from prior experiments. Drug-specific parameters typically include PK parameters, such as intrinsic clearance and volume of distribution and pharmacologic parameters, such as in vivo target affinity and intrinsic efficacy of compounds and

are usually estimated from PK/PD data gathered for the drug [6]. A QSP modeling approach is particularly useful to answer more mechanistic questions for complex biotherapeutic modalities in oncology, which have intricate mechanisms of action and can require multiscale predictions.

In this thesis, the use of modeling and simulation, spanning the continuum from PK/PD to QSP modeling, was explored to help with quantitative decision making in oncology drug discovery and development. The type of model used in each case was dependent upon on the question asked (introduced in **Chapter 1)**. For example, a more statistical population-pharmacokinetic (pop-PK) modeling approach was used for analysis of a large mAb PK dataset with quantitation of variability (**Chapter 2**). Pharmacokinetic/ pharmacodynamic (PK/PD) modeling was used for data driven interpolation of in vitro and in vivo datasets with limited extrapolation (**Chapters 3 & 4**). Quantitative systems pharmacology (QSP) modeling was used to answer more complex mechanistic questions, involving integration of data from disparate sources (literature, in vitro, in vivo and the clinic), linkage of drug pharmacology to biological systems and disease, and multi-scale predictions (**Chapters 4, 5, 6 & 7**). Several key observations and learnings were made, which are discussed further in the sections below.

8.2 Use of mechanistic modeling to reduce animal use

An important finding was that use of modeling and simulation can reduce animal experimentation. In **Chapter 2**, a population PK analysis was completed on 27 mAbs in humans, cynomolgus monkey and in hFcRn transgenic (Tg32) mice and showed that a single set of typical linear PK parameters could be estimated across species with values similar to endogenous IgG [8]. These parameters could be used to inform initial parameters for PK/PD modeling and for simulations to optimize in vivo and first-in-human study designs. Importantly, knowledge of these parameters across species could be used to avoid unnecessary in vivo PK studies. Different translational strategies were also investigated for prediction of human linear PK of mAbs. Use of 'typical' human PK parameters gave good prediction accuracy for the majority of the mAbs in this study and for a test set of different mAbs with linear PK in the clinic. Allometric exponents were estimated within the pop-PK model and also gave good predictions, from both Tg32 mouse and cynomolgus monkey to human. Outliers with higher than typical clearance were found to have non-specific interactions in an affinity-capture self-interaction nanoparticle spectroscopy assay, offering a potential tool to screen out these mAbs at an early stage. The strategies presented call into question the value of completing extensive in vivo preclinical PK for mAbs with linear CL and encourage refinement of PK strategies consistent with the '3Rs', i.e., the reduction, refinement and replacement of animal use in research, testing and teaching [9]. This analysis provides alternatives to the use of cynomolgus monkey for PK prediction, including allometric scaling from Tg32 mouse, or use of human pop-PK parameters as a replacement to animal-based methods [8]. As such, it has the potential to reduce the numbers of cynomolgus monkey PK studies completed.

In **Chapter 3**, a PK/PD modeling approach was used to establish in vitro to in vivo correlations (IVIVC) for antibody drug conjugates (ADCs) [10]. In vitro cytotoxicity assays and mouse tumor xenograft models are the most widely used experimental systems in the preclinical development of oncology drugs. These experiments are very informative to determine drug potency and

efficacy, but no subsequent attempt has been made to integrate the information from these two systems to establish IVIVC for chemotherapeutic drugs. This is exacerbated by the fact that the in vitro and in vivo experiments are completed under different conditions, with different endpoints measured. To establish IVIVC, we determined in vitro efficacy of 19 ADCs using a kinetic cell cytotoxicity assay and determined the viability of cancer cells at multiple timepoints after incubation with various concentrations of ADCs. The data was fitted using a semi-mechanistic PK/PD model, and a secondary parameter called the in vitro tumor static concentration was estimated ($TSC_{in\ vitro}$), representing the concentration of ADC which would result in the cancer cells neither proliferating or decreasing, but held in stasis. The in vivo efficacy of ADCs was evaluated using tumor growth inhibition (TGI) studies performed on human tumor xenograft bearing mice. The TGI and PK data obtained from in vivo studies were characterized using a PK/PD model, parameter estimates from which were used to derive the in vivo TSC ($TSC_{in\ vivo}$), which was the concentration of ADC which would result in the tumor in the mouse neither growing nor regressing. The $TSC_{in\ vitro}$ and $TSC_{in\ vivo}$ values were found to correlate with a Spearman's rank correlation co-efficient of 0.82. On average TSC in vivo was found to be approximately 27 times higher than TSC in vitro, which roughly accounts for tumor penetration. The reasonable IVIVC for ADCs suggests that in vitro efficacy data was correctly able to differentiate ADCs for their in vivo efficacy. Thus, IVIVC can be used as a tool to triage ADC molecules in the discovery stage, thereby preventing unnecessary in vivo testing of ADCs. An ability to predict the concentration of ADC that is efficacious in vivo using the in vitro data can also help in optimizing the experimental design of preclinical efficacy studies. As such, the novel PK/PD modeling method presented here to establish IVIVC for ADCs holds promise for anticancer agents.

Key Learnings:

1. *Think before doing the in vivo experiment!*
2. *Modeling can be a useful tool to reduce animal experimentation, by enabling in vitro to in vivo correlations or use of simulation to replace experimental methodologies.*

8.3 Use of mechanistic modeling for preclinical to clinical translation

One of the key themes explored in this thesis was the use of modeling to translate from preclinical studies to the clinic. One reason to translate to human is to ensure that the best drug, in terms of predicted efficacy and safety, is being progressed to clinical trials. Another important reason is to ensure the most efficient design of clinical dose escalation studies, with the objective of minimizing risk to trial participants while acknowledging the need to quickly escalate to pharmacologically active doses.

The workhorse preclinical model in oncology is the mouse xenograft model, which comprises subcutaneous implantation of a human cell line or tumor into immune compromised host mice [11]. The xenograft model represents extreme simplification of human cancer, as it does not account for complexities of tumor metastasis, host immunity, tumor heterogeneity, and the development of treatment resistance that is routinely observed in cancer patients [12]. However, the drug exposure response relationship derived from these models is useful for understanding efficacy and if accompanied by rigorous quantitative analysis such as mathematical modeling,

can be used to translate from mouse to human to predict clinical anti-tumor response [13, 14]. A rigorous unifying preclinical to clinical translational framework could facilitate oncology clinical development by better identifying translational strategies, patient selection criteria and appropriate biomarkers to measure [15].

In **Chapter 4**, a PK/PD modeling and simulation approach was used for quantitative comparison of a new generation HER2 antibody drug conjugate (ADC, PF-06804103) with the clinical-standard-of-care trastuzumab-DM1 (T-DM1), to ensure that PF-06804103 would provide benefit if progressed to the clinic [16]. To compare preclinical efficacy, the PK/PD relationship of PF-06804103 and T-DM1 was determined across a range of mouse tumor xenograft models, using a tumor growth inhibition model. A secondary parameter, tumor static concentration (TSC), was calculated from the model parameters and defined as the minimal efficacious concentration. From comparison of TSCs, PF-06804103 was concluded to be more potent than T-DM1 across the cell lines studied, with TSCs ranging from 1.0 to 9.8 μg/mL (n = 7) for PF-06804103 and from 4.7 to 29 μg/mL (n = 5) for T-DM1. In addition, two experimental models which were resistant to T-DM1, responded to PF-06804103 treatment.
To translate to the clinic, first a mechanism-based target mediated drug disposition (TMDD) model was used to predict the human PK of PF-06804103. This model was constructed and validated based on T-DM1 which has non-linear PK at doses administered in the clinic, driven by binding to shed HER2. The predicted PK was incorporated into the mouse model and used to perform simulations of tumor regression at different dose levels for PF-06804103 and T-DM1. The model simulations accurately predicted the efficacious dose of T-DM1 and predicted efficacy at lower doses for PF-06804103 in the clinic. In this case, a fit-for-purpose translational strategy was deemed applicable to predict efficacy of two drugs with the same target and mechanism of action, which had been studied in the same experimental models. In addition, the availability of clinical data for T-DM1 was used to validate the modeling and to de-risk translation of PF-06804103 [16].

In **Chapters 5 and 6** more mechanistic QSP strategies are applied for translating from preclinical studies to the clinic, for ADCs and CD3 bispecific antibodies, respectively. In **Chapter 5**, a mechanistic QSP model was developed and used for preclinical to clinical translation of inotuzumab, a CD22 targeting ADC for B cell malignancies including non-Hodgkin's lymphoma (NHL) and acute lymphocytic leukemia (ALL) [17]. The model incorporates more of the mechanistic steps in the causal pathway between drug administration and efficacy compared to the model described in **Chapter 4**. These included (1) a plasma PK model characterizing disposition and clearance of inotuzumab and its released payload N-Ac-γ-calicheamicin DMH, (2) a tumor disposition model describing ADC diffusion into the tumor extracellular environment, (3) a cellular model describing inotuzumab binding to CD22, internalization, intracellular payload release, binding to DNA, or efflux from the tumor cell, and (4) tumor growth and regression driven by payload concentration. Preclinical data in mouse xenograft models for NHL and ALL, were modeled first and then translated to the clinic by incorporating human PK for inotuzumab and clinically relevant tumor volumes, tumor growth rates, and values for CD22 expression in the relevant patient populations. Clinical trial simulations were performed with 1000 patients simulated per dose level, incorporating variability in model parameters representing different

drug, patient, and disease characteristics. The resulting stochastic models predicted progression-free survival (PFS) rates for inotuzumab in patients comparable to the observed clinical results. The more mechanistic nature of the model meant that it could be used for specific quantitative questions, including optimization of dosing regimens for NHL and ALL, and to examine sensitive parameters impacting efficacy in the clinic which could be used to inform clinical diagnostics or potential biomarkers [17].

In **Chapter 6**, a translational QSP model was presented for CD3 bispecific molecules, which integrates in silico, in vitro and in vivo data in a mechanistic framework, to quantify and predict efficacy across species [18]. CD3 bispecific antibodies bind to CD3 on the surface of T cells and a tumor associated antigen on the surface of tumor cells to form a trimolecular complex (hereafter trimer), which mimics an immune synapse. Trimer formation triggers T cell activation, release of perforin and granzyme B which results in cytotoxicity. The proposed QSP model was capable of predicting trimer formation and linking it to tumor cell killing. The model was used to quantify the PK/PD relationship of a CD3 bispecific antibody targeting P-cadherin (PF-06671008). It describes the disposition of PF-06671008 in the central compartment and tumor in mouse xenograft models, including binding to target and T cells in the tumor to form the trimer. The model incorporates T cell distribution to the tumor, proliferation, and contraction. PK/PD parameters were estimated for PF-06671008 and a tumor stasis concentration (TSC) was calculated as an estimate of minimum efficacious trimer concentration. The model was translated to the clinic by incorporating predicted PF-06671008 human PK, including binding to soluble P-cadherin, and clinically relevant system parameters such as CD3 and P cadherin receptor expressions, numbers of T cells and tumor cells. The model was used to predict clinical PK and efficacy, and to determine sensitive parameters affecting clinical efficacious doses[18].

Key Learnings:

1. *When dealing with complex biological systems with multiple variables and pathways, it is advisable to build a mathematical model of the system, capable of integrating and interpreting preclinical data and providing a quantitative framework for translation to the clinic.*
2. *Choose the appropriately sized model and level of translational strategy for the question asked.*
3. *It is possible to translate from mouse xenograft studies to the clinic, if accompanied by rigorous, systematic quantitative analysis, which accounts for differences between the mouse experimental system and the clinic, as afforded by mathematical modeling.*
4. *Mechanistic QSP types of models are an investment in terms of data requirements and development time; however, they offer a high return of investment with respect to the granularity of the questions answered.*
5. *Deterministic models can be combined with stochastic simulations (e.g. virtual patient simulations) to predict efficacy endpoints such as RECIST criteria.*

8.4 Use of mechanistic modeling to optimize clinical dosing regimens

An important topic explored in this thesis was the use of mechanistic modeling and simulation to optimize the design of clinical dosing regimens. This included selection of clinical starting dose using a minimal anticipated biological effect level (MABEL) approach, prediction of clinical efficacious dose and regimen and identification of factors impacting variability in efficacious dose. As discussed above, in **Chapters 5 and 6**, mechanistic QSP models were developed and used to predict efficacious doses for an ADC (inotuzumab) and a CD3 bispecific molecule (P-cad LP-DART), respectively. For inotuzumab, different versions of the model were developed for treating hematological tumors such as ALL and solid tumors such as NHL, differing in their description of tumor disposition, and also in the typical tumor characteristics such as tumor growth rates and initial tumor volumes. The model was ultimately used to recommend a fractionated dosing regimen for ALL, which was predicted to be more tumor regressive compared to the standard Q4w regimen that was used to treat NHL [17].

In **Chapter 7**, a QSP modeling approach to select minimal anticipated biological effect level (MABEL)-based clinical starting dose of bispecific antibodies (bsAbs) was introduced. The approach is based on tumor trimer concentrations driving efficacy and normalizes for differences between in vitro experimental conditions and the clinic. The method was used to predict clinical starting doses of a P-cadherin/ CD3 bsAb. First, a mechanistic in vitro model was constructed which linked predicted trimer concentration and in vitro T cell kinetic and cytotoxicity experiments to determine EC_{20} of trimer driving T cell proliferation and tumor cell killing. The model was able to capture in vitro data at various E:T ratios using the same EC_{20} value. This in vitro MABEL was then translated to the in vivo MABEL to predict human MABEL dose, by incorporation of predicted human PK (including binding to soluble P-cadherin) and physiological parameters (described above). The MABEL human dose was determined as the predicted average tumor trimer concentration at steady-state equal to the in vitro MABEL (EC_{20}, trimer). This method was compared to orthogonal approaches, including PK based methods and receptor occupancy. The QSP-based approach was concluded to give the most appropriate starting dose to balance safety and efficacy, which was independent of experimental conditions [19].

Key Learnings:

1. *QSP modeling can be used to predict optimal dose and regimens for different oncology indications such as hematological versus solid tumors.*
2. *QSP modeling provides an alternative method to predict MABEL-based clinical starting doses which is less dependent on experimental conditions.*

8.5 Use of mechanistic modeling to address precision medicine questions

Another theme explored in this work, was the use of QSP modeling to investigate factors which may impact drug dosing and scheduling in oncology and to identify patients who may best respond to a therapy. Consistent with a precision medicine-based approach this information could be fundamental in the selection of suitable diagnostics and biomarkers to explore in the clinic to optimize therapeutic strategies in oncology [20].
In **Chapter 5**, a QSP model was developed for inotuzumab, a CD22-targetting ADC for B-cell malignancies [17]. The model was used for preclinical to clinical translation and to optimize doses

and regimens for a new indication being explored (ALL) versus the original indication (NHL). Development of inotuzumab for r/r NHL had recently been terminated due to lack of superiority versus standard of care. A sensitivity analysis was performed to give insight into the parameters defining, or even limiting, efficacy of inotuzumab versus NHL. CD22 receptor expression, calicheamicin efflux rate, inotuzumab PK (clearance rate), and tumor growth rate were selected as relevant parameters to vary in the model. Tumor growth rate was found to be the most sensitive parameter and suggested that for the more aggressive NHL sub-types like diffuse large B cell lymphoma (DLBCL) patients would require significantly higher doses for efficacy, compared with slower growing NHL sub-types such as follicular lymphoma. Calicheamicin efflux from the tumor cell was a sensitive parameter, which is important as N-Ac-γ-calicheamicin DMH is known to be a substrate for MDR1, an efflux transporter which is upregulated on many tumor-cell types. The least sensitive parameter was CD22 receptor expression which indicated the suitability of this receptor as an ADC target due to its high expression across B cells and rapid internalization rate. These findings suggest that MDR1 status in patients would be a more useful diagnostic of efficacy than CD22 receptor expression.

A similar approach was taken in **Chapter 6**, where a sensitivity analysis was used to determine key parameters impacting predicted clinical efficacious dose for P-cad LP-DART, a CD3 bispecific antibody [18]. The analysis showed that P-cad expression was a sensitive parameter with a higher dose required for patients exhibiting low P-cadherin expression. T cell number in the tumor was also a sensitive parameter with a higher predicted dose required for efficacy at low effector: target cell ratios. In conclusion, use of mathematical modeling and the strategies discussed above, can facilitate decisions on the most appropriate drugs for a given patient, help optimize dosing and combination regimens, and propose alternative and improved schedules of administration.

Key Learnings:

1. *QSP modeling can be used, via sensitivity analysis and simulations, to identify key parameters impacting outcome in the clinic.*

8.6 Platforms models for biotherapeutic modalities

Two models described in this thesis: the ADC QSP model (**Chapter 5**) and the CD3 bispecific model (**Chapter 6**) are potential platform models for specific biotherapeutic modalities in oncology. These are QSP models which provide a common integrated quantitative knowledge repository for continued preclinical and clinical evaluation [21]. They are not specific to a particular drug and therefore can be re-applied, providing a mechanistic framework for predicting efficacy distinct from other pharmacometrics strategies [21]. They are often multiscale and modular, and can be used to characterize in vitro, preclinical in vivo and clinical data. As such, they can be used to support program decision from exploratory research through to late-stage clinical trials. Platform models can be an investment in terms of data requirements, but they offer a high return of investment with respect to the granularity of the questions answered.

The ADC QSP model describes the intricate mechanism of action of ADCs including characterization of ADC and payload disposition at the cellular and physiological level to predict the clinical outcome of ADCs [17]. The model describes (1) plasma PK including disposition and clearance of ADC and released payload, (2) a tumor disposition model describing ADC and payload diffusion into the tumor extracellular environment, (3) a cellular model describing ADC binding to its target on tumor cells, internalization, intracellular payload release, payload binding to its target, payload efflux from the tumor cell, and (4) tumor growth and inhibition in mouse xenograft models as a function of tumor payload concentration.
The CD3 bispecific antibody (bsAb) model is a potential platform model for immune cell engaging bsAbs which act to cross-link a tumor cell with an immune effector cell to redirect cytotoxicity against the tumor cell [18]. The current model was used to characterize a bispecific molecule binding to CD3 on T cells and P-cadherin on tumor cells (Pcad-LP-DART) [18]. The model describes (1) plasma PK, including bsAb binding to soluble target and circulating T cells in the systemic circulation (2) a tumor disposition model describing bsAb diffusion into the tumor (3) binding of the bsAb to T cells and tumor cells to form dimers and trimers (4) T cell distribution to the tumor, proliferation, and contraction and (5) tumor growth and inhibition in mouse xenograft models as a function of tumor trimer concentration.

These platform models can be used for diverse purposes such as:

1. Optimizing design of ADCs or CD3 bsAbs at early stages to enable maximal chances of success.
2. Design and interpretation of preclinical in vitro and in vivo experiments for efficient and effective lead selection.
3. Translation of preclinical data to the clinic to predict clinical efficacious dose and regimen.
4. Prediction of drug response (e.g. tumor growth inhibition, RECIST criteria) and optimization of dose and regimen for different oncology indications.
5. Understanding variability to drug response in the clinic and use of this information for selection of suitable diagnostics to inform patient selection and clinical biomarkers to monitor for earlier signs of efficacy.
6. Comparison against clinical standard of care.

In addition, the current model structures have the potential to be expanded to predict toxicities associated with the mechanism of action. For example, the ADC model could be expanded to describe ADC uptake and release of payload in megakaryocytes and platelets to quantify typically observed ADC toxicities such as neutropenia and thrombocytopenia. The CD3 bsAb model could be expanded to relate trimer formation to cytokine release to predict cytokine release syndrome. Finally, both models could be extended to predict combination therapy treatments. For example, this could include addition of an immunotherapy model to predict combination with checkpoint inhibitors such as anti-PD1 mAbs.

Key Learnings:

1. *Platform QSP models are amenable to reuse and repurposing to support diverse decisions from early drug discovery through to clinical studies.*

8.7 Conclusions and future perspectives

In this thesis, mathematical modeling and simulation was applied as a tool to inform quantitative decision making in oncology drug discovery and development. Modeling based approaches were shown to be useful to understand the mechanism of action and deconvolve the complexities of novel biotherapeutic modalities being used to treat cancer, including monospecific and bispecific monoclonal antibodies and antibody drug conjugates. Several key observations and learnings were made. For example, modeling was shown to be a useful method to reduce animal experimentation, by enabling in vitro to in vivo correlations or use of simulation to replace experimental methodologies. Mechanism based modeling and simulation was found to be a useful means to translate from preclinical studies to the clinic to ensure progression of the best drug to clinical trials. These models could then be used to optimize design of clinical studies from selection of starting doses to recommended efficacious doses for pivotal trials. Modeling was shown to be beneficial to understand variability in the clinic and to identify factors impacting drug response in individual patients, paving the way for precision medicine strategies, informing clinical diagnostics, biomarkers, and doses for different oncology indications. Finally, the ADC QSP and CD3 bsAb models were identified as potential platform models amenable to reuse and repurposing to support diverse decisions across the drug discovery and development continuum.

Oncology drug discovery and development will get more complex, as we continue to unveil more of the intricate aspects of tumor biology and the pleiotropic role of the immune system. In parallel, the complexity of biological therapies will continue to evolve, with the introduction of multi-specific antibodies targeting several receptors and modulating different pathways, novel cell therapies, and multiple drug combinations leading to novel biological effects and synergies. As a result, mechanistic modeling and simulation will become an essential cornerstone of oncology drug discovery and development, to understand the often-non-intuitive processes and to aid in rational decision making. To facilitate this process, it will be imperative to apply modeling and simulation earlier in the drug discovery process to facilitate success and ensure reduced attrition rates later in clinical studies. There will be increasing opportunities to combine QSP modeling with emerging technologies. Undoubtedly integration of big data technology and data science (including crowd sourcing and machine learning) with QSP modeling will play an important role in the application of mathematical modeling for decision making within oncology drug research. Thus, the wealth of emerging genomics and biomarker data will be applied to maximize the power of QSP modeling to help ensure patients get the best possible treatment.

8.8 References

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