Planning a Phase 1 Clinical Trial: Target Product Profile for a Novel Target CAR T-cell Therapy

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Background

- Chimeric antigen receptor (CAR) T-cells are genetically engineered immune cells commercially available to treat B-cell lymphoma.
- After CD19 CART treatment, half of patients relapse within 6 months due to downregulation of the CD19 antigen and tumor resistance, leading to a need to develop novel treatments.[3]
- Developing new therapies is a process that takes years. The FDA requires the development history to be summarized in a document called a Target Product Profile (TPP). A TPP is a live document following a drug from preclinical to commercial that collects all its clinical and production information.
- The development of any new therapy starts with a risk-benefit approach (Figure 1), followed by the actual development of the drug (Figure 2).

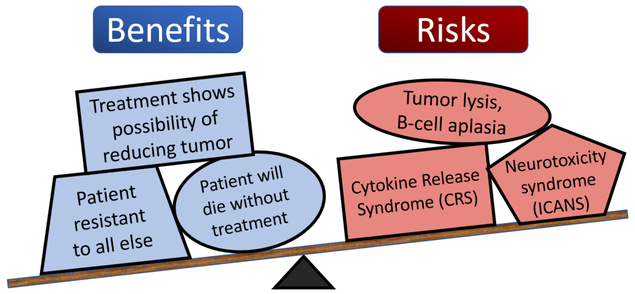

Figure 1. FDA assessment of a drug depends on the balance of risks and benefits..[2,4]

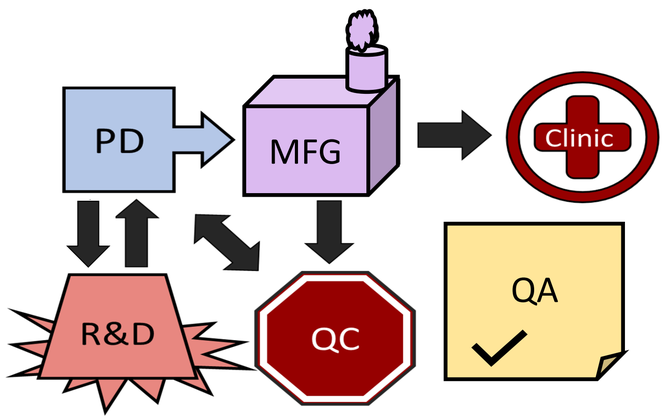

Figure 2. Process of developing, manufacturing, and releasing a biologic drug at MD Anderson.

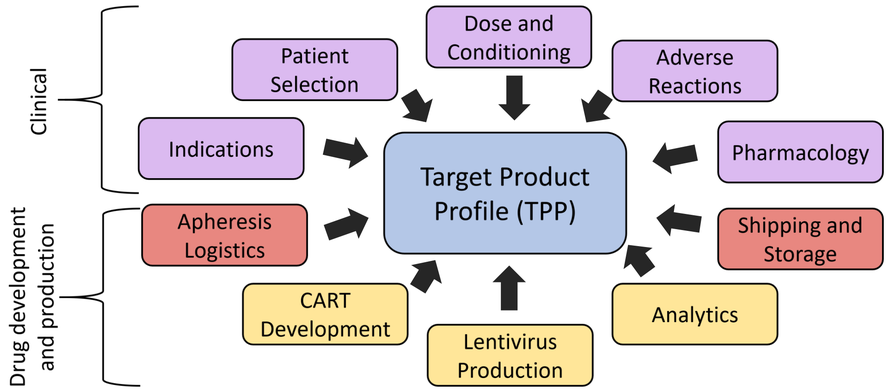

Figure 3. Components of the clinical and production sections of the novel target CAR T-cell Target Product Profile (TPP).[1]

Construction of a TPP

The TPP is a live document that follows a drug through its development process and records all relevant information.

- The TPP contains both clinical and drug development/production information.
  - Clinical information includes indications, patient eligibility criteria, dosing and pre-treatment conditioning, expected adverse reactions, and pharmacology.
  - Drug development covers CART and lentivirus production, as well as analytics and release testing. Production logistics are also included.

- Met with each team member to compile information.
- Observed the laboratory steps in the development process.
- Conducted a literature review of CAR T cell therapy research to provide a description of pharmacology, likely adverse reactions, contraindication, and drug interactions.
- Collected information about upcoming dose escalation and expansion clinical trial, release testing and qualification requirements, and clinical procedure.
- Constructed a detailed process description.

References

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3. Martino, M.; Alati, C.; Canale, F.A.; Musuraca, G.; Martinelli, G.; Cerchione, C. (2021). *Int. J. Mol. Sci.* 22(4), 2150.
4. Neelapu, S.S.; Tummala, S.; Kebriaei, P.; Wierda, W.; Gutierrez, C.; Locke, F.L.; Komanduri, K.V.; Lin, Y.; Jain, N.; Daver, N.; Westin, J.; Gulbis, A.M.; Loghin, M.E.; de Groot, J.F.; Adkins, S.; Davis, S.E.; Rezvani, K.; Hwu, P.; Shpall, E.J. (2017). *Nat. Rev. Clin. Oncol.* 15, 47-52.

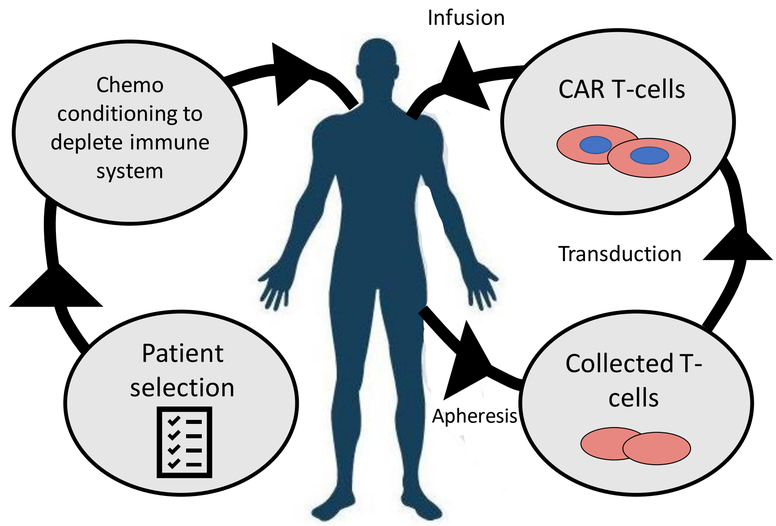

Figure 4. Procedures for CAR T-cell treatment. The patient is selected from eligibility criteria and conditioned, while T-cells are collected, genetically modified, and infused back into the patient.

The Clinical Product – Result of the TPP

Manufacturing Procedure

1. Autologous T-cells are collected through apheresis.
2. T-cells are isolated through immunomagnetic cell separation.
3. T-cells are activated with antibodies and IL-2.
4. T-cells are transduced with a lentiviral vector to express the intended CAR.
5. CAR T-cells are expanded with media and IL-2 for 2-3 days until dose level is reached.
6. CAR T-cells are harvested and cryopreserved.

Clinical Procedure

1. Patient undergoes leukapheresis.
2. Patient receives chemotherapy conditioning to deplete the immune system and allow space for CAR T-cells to proliferate.
3. Patient receives a single infusion of a fixed dose of CAR T cells.
4. Patient is monitored daily for two weeks after infusion.

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