Comments on "Cost of decentralized CAR T cell production in an academic non-profit setting"

Dear Editor-in-chief,

We would like to comment on the article "Cost of decentralized CAR T cell production in an academic non-profit setting" by Ran T et al. [1] published in your prestigious journal on June 14, 2020. This article touches a very sensitive topic which is currently under hot debate between CAR-T cell manufacturing University Hospitals and health care payers in Germany.

We have produced almost 30 clinical grade CD19-directed chimeric antigen receptor (CAR) T cell products for our clinical trial within the last 2 years. These products were generated within an identical state and federal regulatory framework as anticipated by Ran et al. for their model. However, our experience in terms of real-life financial effort for production of good manufacturing practice (GMP)-grade CAR T cell products differs dramatically from that calculated by the authors. These differences apply to all steps of production and clinical development as detailed in the following.

Manufacturing

- For the establishment of a CAR T cell production process under GMP conditions, a GMP clean room grade B is required. The annual fixed costs for qualification and maintenance of a clean room grade B are mentioned in Table 1. In our practical experience, however, the costs for this requirement are almost three times as high.
- Next, CAR-T cell production devices have to be procured. In the article the ClinicMACS Prodigy™ device from Miltenyi is mentioned, which currently costs 250,000 EUR with additional annual maintenance costs of 16,500 EUR. Other mandatory devices include clean room refrigerator, clean room -20°C freezer, microscope, non-clean room refrigerator, -20°C freezer, -80°C freezer, cryopreservation device with respective nitrogen tank capacity and the required replacement devices in case of device failure. For quality control at least microscope, centrifuge, flow cytometer, polymerase chain reaction (PCR) device and incubator are required. All these devices have to get an annual maintenance check. These efforts are not realistically reflected by the cost estimations in Table 1.
- For the establishment and maintenance of a clinical-grade CAR T cell production process continuous validation is mandatory, such as validation runs for the CAR T cell production, media fill runs, validation runs for all quality control assays in-house as well as for external quality control assays. Comprehensive validation is cost intensive and must be considered in the cost calculation, including eventualities such as repeat validation if there is a change in any ingredient needed for production.
- Moreover, legal and good clinical practice (GCP) requirements stipulate that for manufacturing of any clinical-grade cellular product responsible production personnel is required including a head of production, a head of quality control, and a qualified person (QP). As these three positions usually require high qualification, the costs listed in Table 1 should be adjusted accordingly.
- The calculation contains only two experienced technicians. For a production following the 4-eyes principle and with respective quality control personnel this is clearly

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insufficient. At least one additional full time employee is needed for back-up. Therefore, this position does not reflect the real-world costs and should be adjusted.

- In Germany, the time needed for setting up a GMP/GCP-conform CAR T cell production process until receiving the manufacturing authorization takes, as this article correctly suggests, usually at least 2 years. During this time the clean room as well as the devices, personnel, GMP media, substances, material and quality controls have to be financed. This has to be considered in the final product cost calculation.
- For CAR T cell manufacturing a vector produced according to GMP is required. This vector has to be tested in advance in respective assays (f.e. animal models) to prove that it does not harm the patient and that it is functionally active. The costs of a batch, which needs to be broken down and added to the individual product cost, are calculated in the article with 866,666 USD. However, according to practical experience in 2020, actual prices for vector production are at least twice as high, and will take up to 2 years since a master cell bank needs to be established.
- Commercial CAR T cell manufacturers offer products with second generation CAR vectors. However, novel generations of CAR vectors are at the doorstep of clinical application. Unlike commercial manufacturers, academic institutions are sufficiently flexible to align their in-house production capacities in real-time with the rapid CAR and vector development for speeding up improvement of patient care. However, this continuous process is personnel and cost intensive.

Clinical Development

Before use as standard of care, novel CAR T cell products – similar to all drug innovations – have to be tested in clinical studies, putting an enormous additional financial burden on the product provider. These costs include but are not limited to complete clinical trial management, clinical research organization (CRO) costs, investigational product manufacturing, complying with all regulatory requirements, obtaining a multitude of approvals from national and state regulatory authorities, both for clinical trial performance and investigational product manufacturing, etc.

In conclusion, the CART production cost estimates elaborated in the study by Ran et al. grossly differ from real-world experience. Several costly aspects for CAR T cell manufacturing for clinical use were not considered at all in the manuscript. Accordingly, is it possible that the authors simply calculated the costs for a research product and then added a gross estimate of regulatory costs? There is no doubt that scientific modelling has its value, but it needs to be validated by practical evidence and real-world application. In its present form, this study bears the risk of raising unrealistic expectations in the public and on the health care payer side. This may harm patients by impeding clinical development and application of academic CAR T cell therapies.

Abbreviations:
CAR: chimeric antigen receptor, CRO: clinical research organization, GCP: good clinical practice, GMP: good manufacturing practice, PCR: polymerase chain reaction, QP: qualified person.

Conflicts of interest:
Michael Schmitt: Apogenix, Hexal and Novartis (research support). Hexal, Kite/Gilead (travel grants). Bluebird bio, Kite, Novartis (financial support for educational activities and conferences). MSD (advisory board member). MSD, GSK, Kite, BMS ((co-)PI of clinical trials). TolerogenixX Ltd. (co-founder and shareholder).
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