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

Dear Editors,

We have read with interest the comments by Michael Schmitt et al. [1] to our study of the "cost of decentralized CAR T-cell production in an academic setting". [2] While the letter confirms the sensitivity of the topic, in our view it is, at least in part, a result of misunderstandings by its authors. Importantly, our study is not based on "scientific modelling" (as suggested in the letter) but rather on the application of standard cost accounting techniques using empirical data.[3] Our objective has been to increase the transparency of one cost component often cited as a reason for certain pricing policies,[4, 5] and to illuminate the potential to reduce manufacturing cost and improve efficiency offered by an alternative to commercial products and their high acquisition costs. Unfortunately, in their letter, the authors do not contribute to the much-needed transparency,[6] as they claim that in their experience the (undefined) "real-life financial effort … differs dramatically" from our analysis, but do not offer any quantitative information to support their claim.

For clarification, let us first reiterate that our report deals with just one cost component, i.e., the fixed and variable cost arising from decentralized CAR T-cell production in our setting. This should not be confused with pricing and reimbursement policies. Especially in commercial settings, the latter will also be influenced by the cost of research and development, by administrative overheads including marketing and sales expenditures, as well as by the expected return on investment. We note that "clinical development" (the last issue raised in the letter by M. Schmitt et al.[1]) represents a cost category clearly different from the cost of production.

In the absence of transparent information provided in the letter,[1] we cannot explain why its authors experience "dramatically different" and supposedly higher costs. Instead of speculating about potential underlying factors such as degree of process automation and use of modern closed systems, we would like to take this opportunity to explain our calculation by responding to the concerns raised by Schmitt et al.[1] In detail:

- In fact we calculated on the basis of class B clean room conditions; yet, we note that class C clean room conditions are sufficient if and when closed systems are used. Several sites in Germany received manufacturing authorization to produce CAR T cells using closed systems in a class C clean room. While Schmitt et al. assert that clean room grade B was required, this holds – with few exceptions only – in open (and therefore more cost intense) environments, which have been superseded by more advanced closed systems. To the best of our knowledge, none of the CAR T cell products manufactured by Schmitt et al. were processed using a semi-automated closed system.
- Regarding asset-related costs, all equipment mentioned by Schmitt et al. has been taken into account in our calculation. To reflect the value consumption of fixed assets, we used their acquisition costs as depreciation basis and applied useful life spans of between 5 and 13 years, respectively. Consistently, we assumed no residual value of assets thereafter. We did of course include our actual maintenance costs; we recognize however that these may vary depending on service level needed.

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- We have treated the set-up of GMP conforming production processes and initial validation runs as sunk costs. As public sector organization, in that respect not much different from university hospitals, these were born directly or indirectly by institutional or third-party grants, thus in effect by donors and taxpayers. We therefore believe that these costs should be treated as irrelevant for decision-making in publicly-funded, non-commercial environments.
- We included the full costs of responsible personal in our calculation. It stands to reason that we allocated the relevant costs for a Qualified Person (QP), head of production, head of quality control, and so on. For example, we allocated for the QP a 50% position in case of one machine and up to 18 products, 70% for two machines and a full position for three machines. We also included an allowance for a back-up (deputy) QP at five percent of her cost. For the head of production, we calculated one full-time equivalent plus a 10% deputy provision for one machine, again with an increasing allocation if more machines were in operation, and so on. Three technicians were calculated for two or three machines in operation. Of note, our peer reviewers asked us to allocate only the actual working hours of technicians, which we disputed, as the technicians are also busy with maintaining the status of the whole system and thus should be calculated as fixed costs and not as variable costs.
- We have double-checked with our vendors the actual conditions for lentiviral vector production at a quality accepted by the authorities for non-commercial use in clinical trials. Costs for GMP-grade lentiviral vector constructs is at present (2020) still around 866,666 $ including production of the transfer plasmid, of test and GMP batches of the lentiviral vector and control of the product. According to recent experience of customers, the number of transgenic T cell products that can be manufactured with one batch of lentivirus may vary between 20 and 50, in exceptional cases even up to 100. Our conservative estimation of 30 products is thus still valid.
- As to new CAR vectors, we have been working with 3rd generation CAR constructs. We agree that academic institutions have the flexibility to develop new vectors and even completely new CARs (as we do) and can adapt their GMP CAR productions flexibly to these new products. However, we think that development of a new CAR is not part of the production costs but should be subsumed under research expenditures, as it contributes to the dynamic but not to the static efficiency of the process.

In sum, the letter of Schmitt et al. [1] does not contribute to an increased transparency of CAR T cell manufacturing costs. However, although perhaps inadvertently, it illustrates the potential for future cost reductions due to technological improvements ("learning curve effects", such as the use of semi-automated closed systems, as well as non-viral vector systems) and standardization, in addition to economies of scale and scope to be expected in the future.

**List of abbreviations**

CAR chimeric antigen receptor

GMP good manufacturing practice

QP Qualified Person

**Conflict of Interest Statement**

In addition to his primary employment with the DKFZ, MS is Chairman & Scientific Director of the non-profit Institute for Innovation & Valuation in Health Care (InnoVal-HC) in Wiesbaden / Germany, which accepts funding under an unrestricted educational grants policy only. In the context of his involvement with non-cancer-related projects at InnoVal-HC, he has received travel expenses and honoraria for lectures and presentations. The other authors declare no conflict of interest.

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