Wrap-up

Tohru Inoue and Takahiro Nakazawa

Key Takeaways

Item	Takeaway
Basic principle and scope	▪"Case-by-case" concept should be preserved. ▪Bioconjugates are a new category of S6 and need specific considerations. ▪Antisense and RNAi are out-scope of S6.
Species selection	▪Transgenic animals and homologous proteins could be an alternative, however, there are limitations. ▪Safety margin, validation, historical data, not final product and different pharmacology ▪Homologous proteins seem to be more useful alternative than transgenic animals.

Key Takeaways (Cont'd)

Item	Takeaway
Dose selection	▪MABEL would be an option to predict starting dose for FIH from preclinical information. ▪One should note that a too conservative approach would result in slow down of the development of biopharmaceuticals ▪ NOAEL approach has been appropriate for most cases.

Key Takeaways (Cont'd)

Item	Takeaway
Repro/dev tox	▪Monkey repro/dev tox studies are feasible and meet regulatory requirement, although there are some technical difficulties.
HERG assay	▪Most biopharmaceuticals may not block potassium channel because of the failure of penetration of the molecule into cell inside ▪ Some proteins/peptides are reported to inhibit HERG current through binding to toxin binding site or stimulating superoxide, however, these may not the cases for biopharmaceuticals. ▪ If QT prolongation is observed in an *in vivo* study, an *in vitro* study including HERG should be considered.

Key Takeaways (Cont'd)

Item	Takeaway
Genotoxicity testing	▪Genotoxicity risk should be assessed for bioconjugates with a chemical organic linker. ▪If no degradation of a bioconjugate occurs or if there is a precedent of the use of a linker, genotoxicity studies may not be needed.

Key Takeaways (Cont'd)

Item	Takeaway
Carcinogenicity studies	▪Carcinogenicity assessments need to be based on a scientific cause for concern. ▪Pharmacology, data from chronic studies, patient population ▪Alternative approaches (e.g. a chronic tox study in a relevant animal) are useful and justified in many cases. ▪A 2-year rodent bioassay should not be an expectation. ▪Histopathological examination of proliferative changes such as PCNA is recommended. ▪*In vitro* proliferative assays are useful.

Conclusion

- ICH S6 guideline should be updated to reflect accumulated experience of biopharmaceuticals and advanced scientific knowledge.
- The contents discussed in this forum are areas for the update.