

# Can we use platform approaches in the non-clinical development of oligonucleotide-based therapeutics?

*A regulator's perspective*

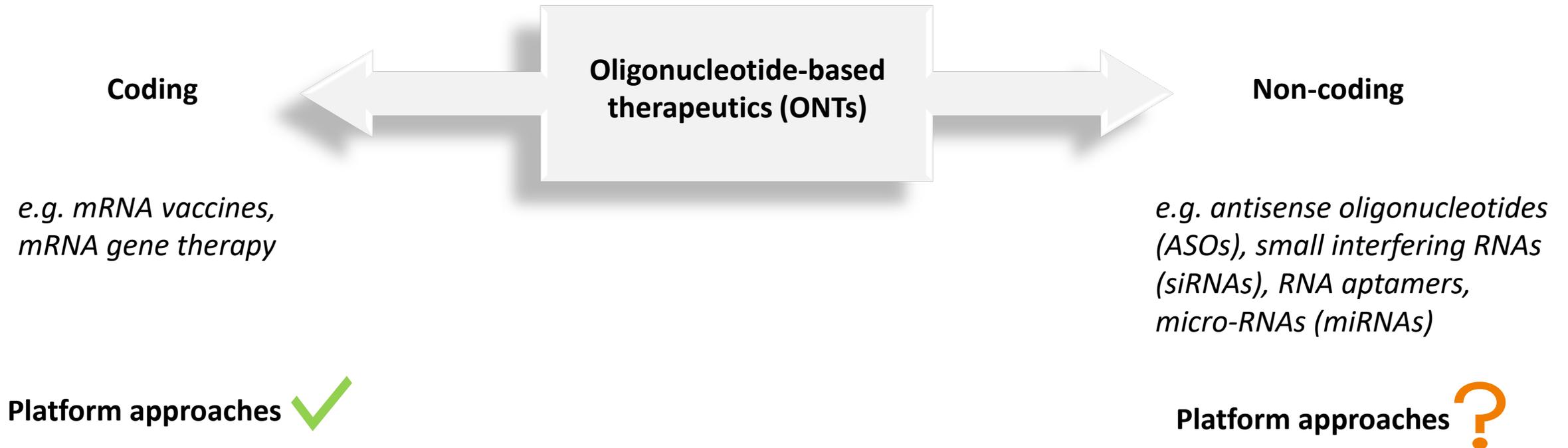
*Britt Duijndam, Non-clinical assessor  
Medicines Evaluation Board, The Netherlands*

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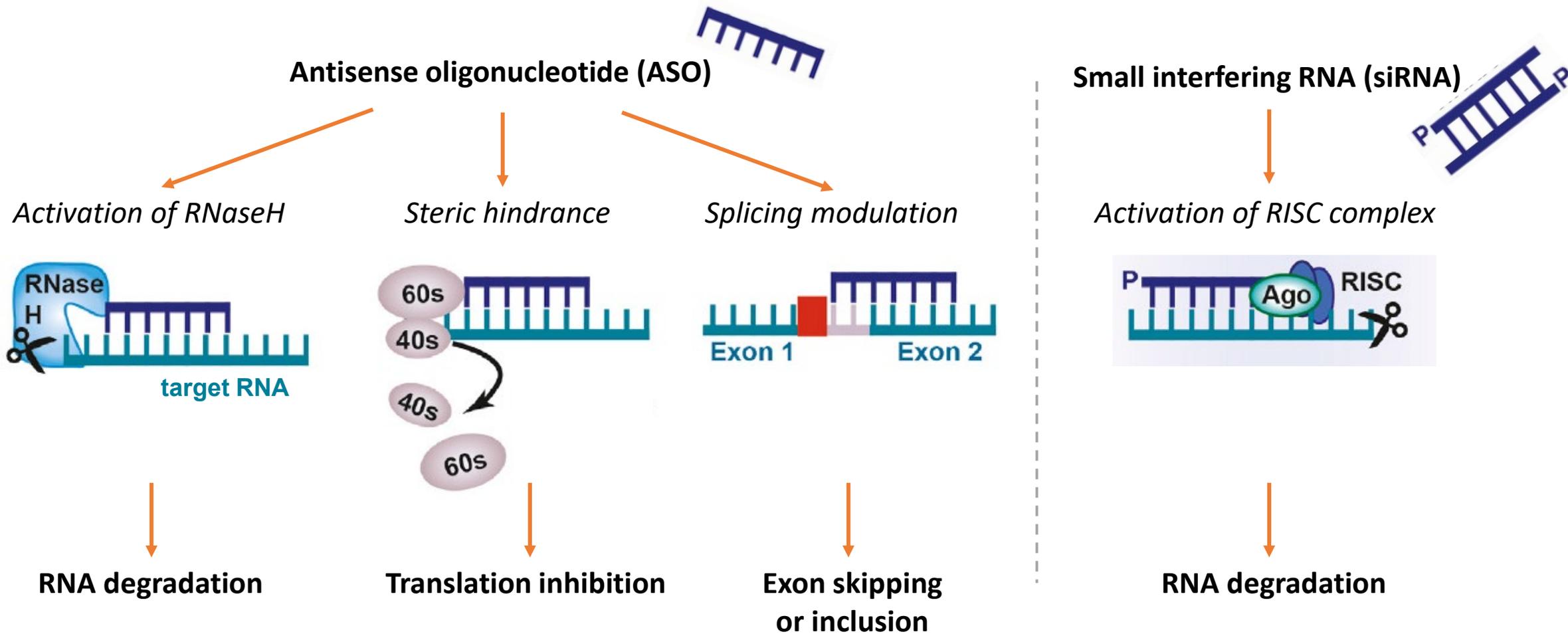
*View presented today is personal and does not necessarily reflect that of the Medicines Evaluation Board.*

# Scope: Non-coding oligonucleotide-based therapeutics

$\frac{C \ B \ G}{M \ E \ B}$

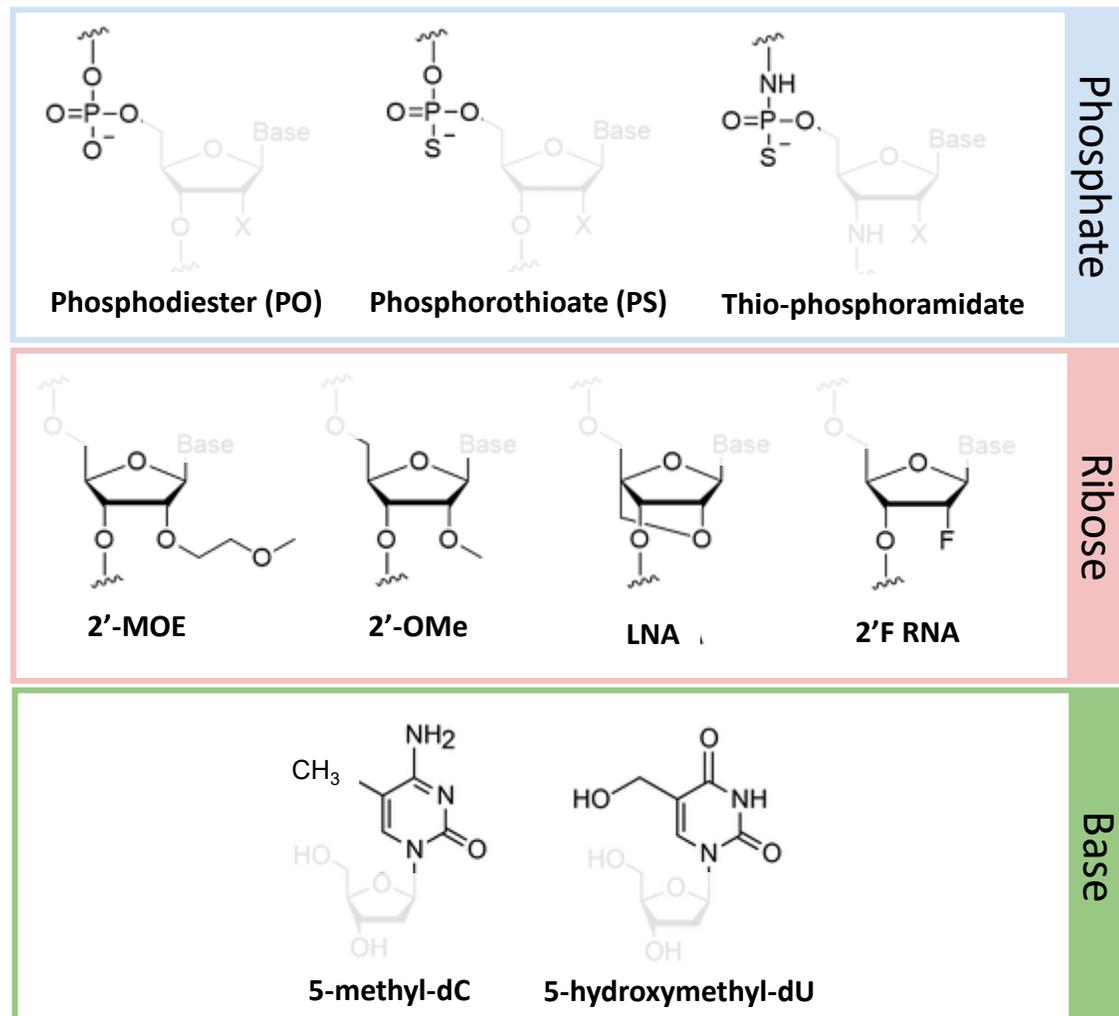
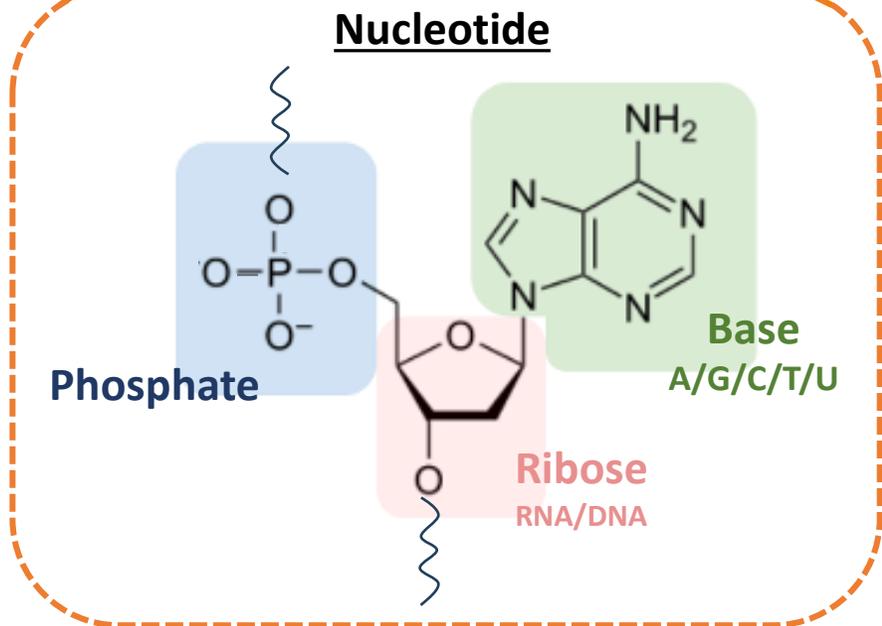
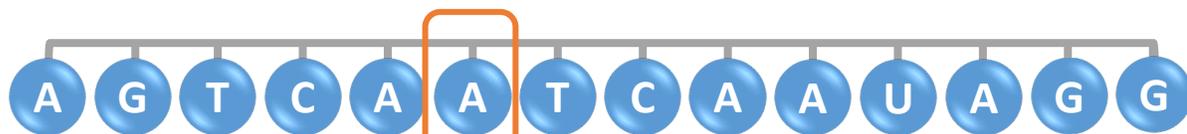


# What are non-coding ONTs, and how do they work?



# Chemical modifications enhance ONT properties

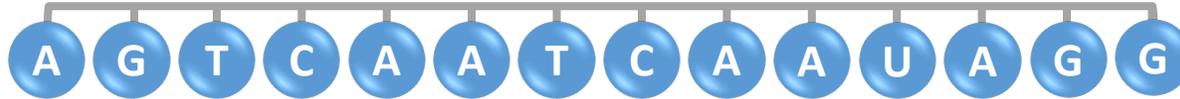
c B G  
M E B



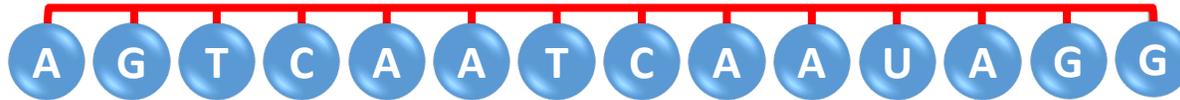
# Platform approach: what is similar? Which differences are important?

$\frac{C \ B \ G}{M \ E \ B}$

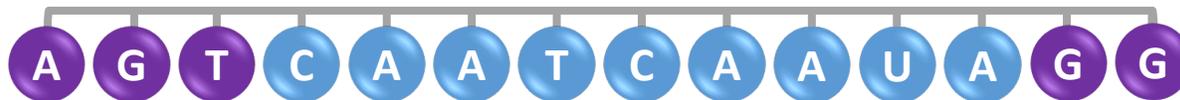
Unmodified



Change phosphate linker



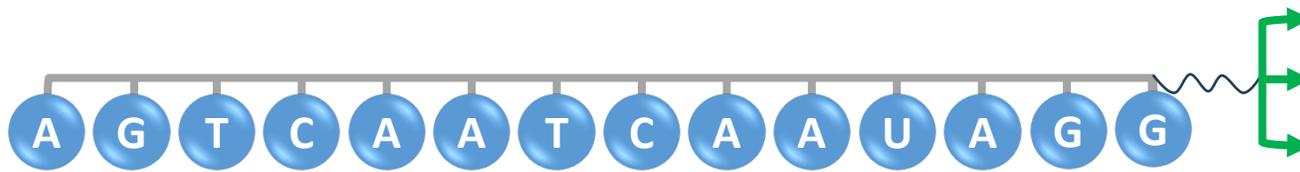
Change ribose



Change sequence



Conjugate to receptor-ligand

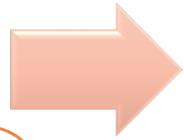


## Similar?

# CBG-MEB project: Identify critical aspects which should be addressed by the upcoming ICH S13 guideline

## Strategy

- Create overview of non-clinical safety testing strategy of ONTs
- Evaluate advice Application position



## Sources

- Initial marketing

### Oligonucleotide-based therapeutics: Hard to handle?

Evaluation of genotoxicity testing from a regulatory perspective  
Clara Stock<sup>1</sup>, Britt Duijndam<sup>1</sup>, Kris Siezen<sup>1</sup>, Anna M.G. Pasmooij<sup>1,2</sup>

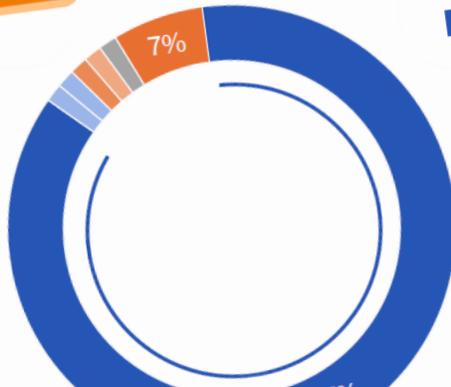
Corresponding email: c.stock@cbg-meb.nl

#### Test strategy

87% performed

Standard battery testing

10%



- No tests (N=5)
- Standard: Ames + in vitro + in vivo (N=66)
- Standard + in vitro or + in vivo (N=2)
- Ames + in vitro (N=1)
- Ames (N=1)
- Unknown

#### Aim

Identify critical aspects of genotoxicity testing of ONTs using non-clinical data and Scientific Advice (ScAdv) positions to inform the process of the ICH S13 drafting group towards a more tailored guideline for ONTs.

#### ONTs



... are chemical synthesized, small (~ 20-30 nucleotides) single- or double stranded nucleic acid- based polymers which modulate gene expression

#### Diversely modified ONTs

Is there a potential genotoxic risk for ONTs?

Main concern: Incorporation of chemical modified monomers into nuclear DNA

ONTs are diversely chemical modified to improve their stability and pharmacological activity

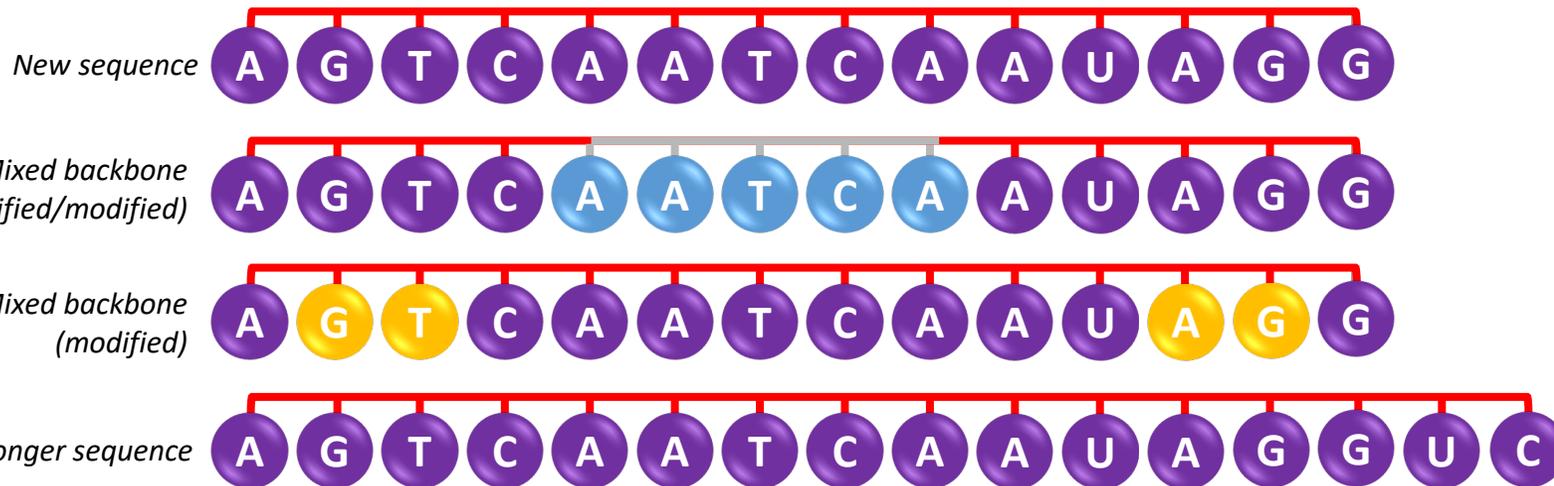
# Genotoxicity assessment: platform-like approach using “well-characterized” modifications

$\frac{C \ B \ G}{M \ E \ B}$

**Main concern for ONTs:** Incorporation of liberated chemically-modified nucleotides into the DNA leading to DNA damage or mutations.<sup>1</sup>



Genotoxicity data available from panel of ONTs with 2'-MOE/PS modifications and different sequences

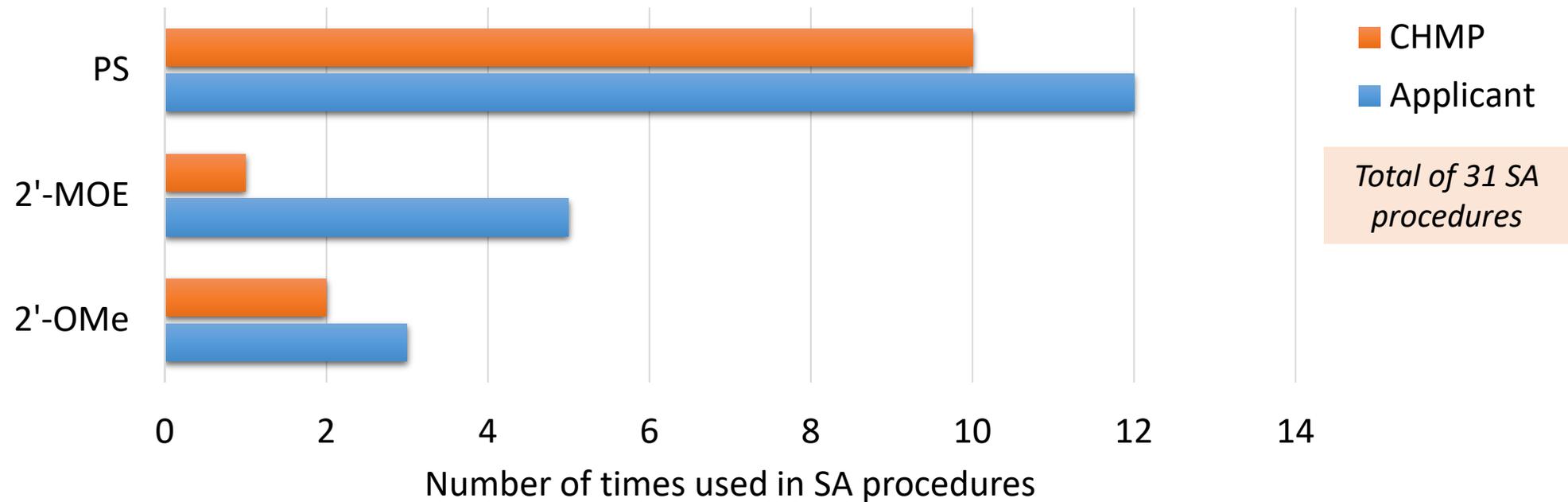


## Similar for genotoxicity?

- ✓ Modifications have been sufficiently tested
- ✓ Unmodified nucleotides are not of concern
- ✗ Introduced “new” modification
- ✓ Modifications have been sufficiently tested

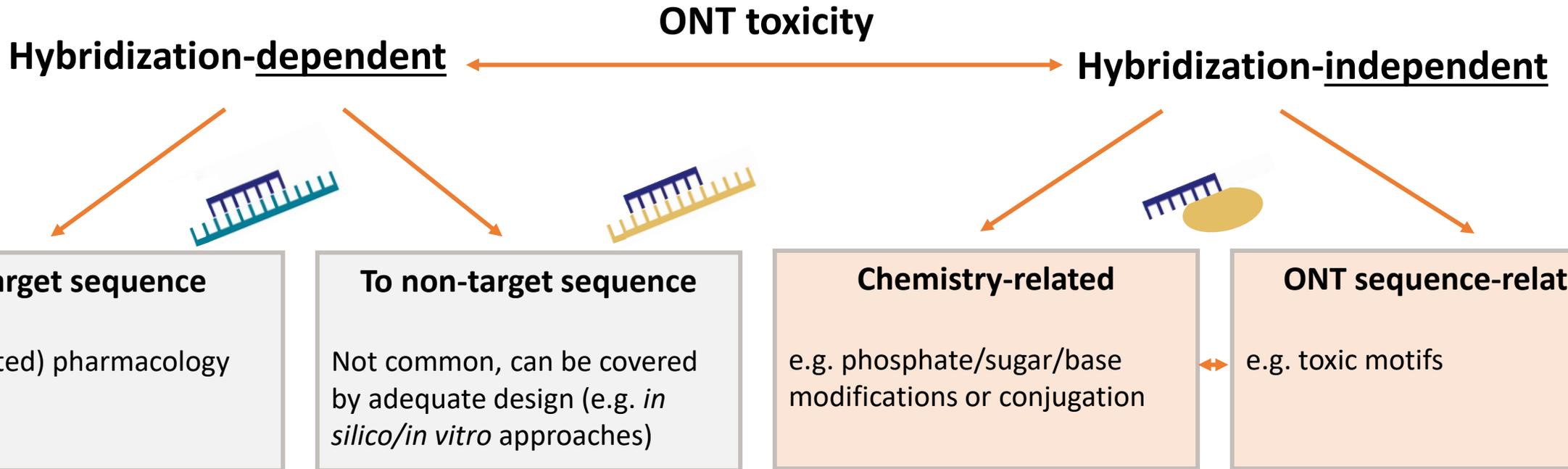
# Platform-like approaches for genotoxicity assessment are discussed, but not always carried out

## Reference to previous experience with modification



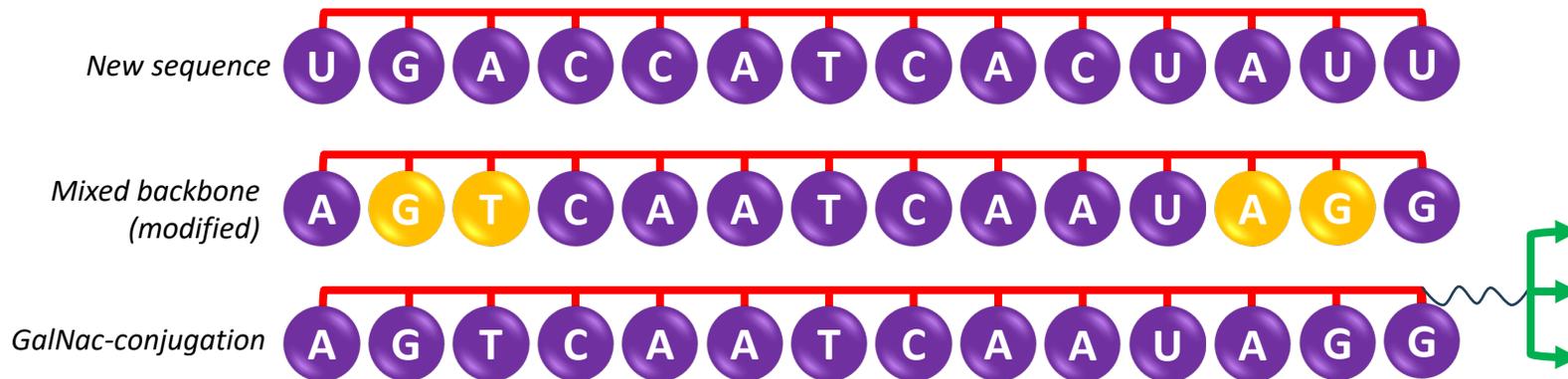
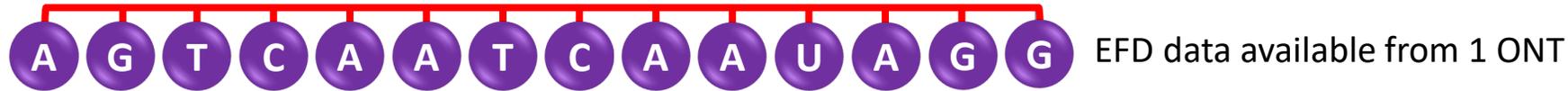
**Only 10% of ONT products (7/76) performed no genotoxicity tests or only a limited set of tests.**

# Which types of toxicity are we concerned about? And how to address them?



**Do we need two species?  
Are there alternative (platform?) approaches?**

**Embryofetal development (EFD) study:** Detect adverse effects on the pregnant female and development of the embryo and foetus following treatment of the pregnant female during organogenesis (in 2 species).



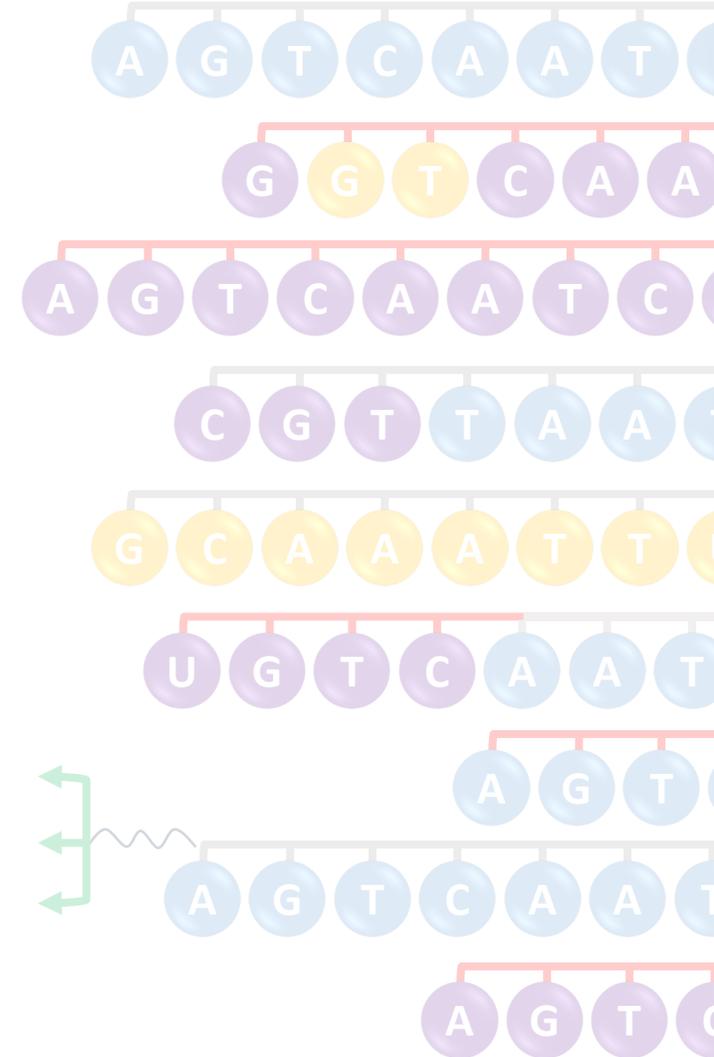
## Similar for EFD?

- ✗ Sequence-related effects insufficiently covered
- ✗ Introduced “new” modification
- ✓ This conjugation does not negatively affect EFD endpoints

# Platform-like approaches are applicable to the non-clinical development of ONTs



- Different platform-like approaches or weight-of-evidence approaches are used for ONTs
  - However, approaches can be different between (toxicological) endpoints
- We should push for scientific justification of studies, and move away from a tick-box-approach.
  - Platform-like approaches can justify a leaner set of animal studies, in line with 3Rs principle (i.e. the reduction, refinement and replacement of animal studies)
- What do we need as regulators? More data...
  - To facilitate “similarity” discussion and substantiate platform approach
  - To support development of other alternative (non-animal) approaches





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