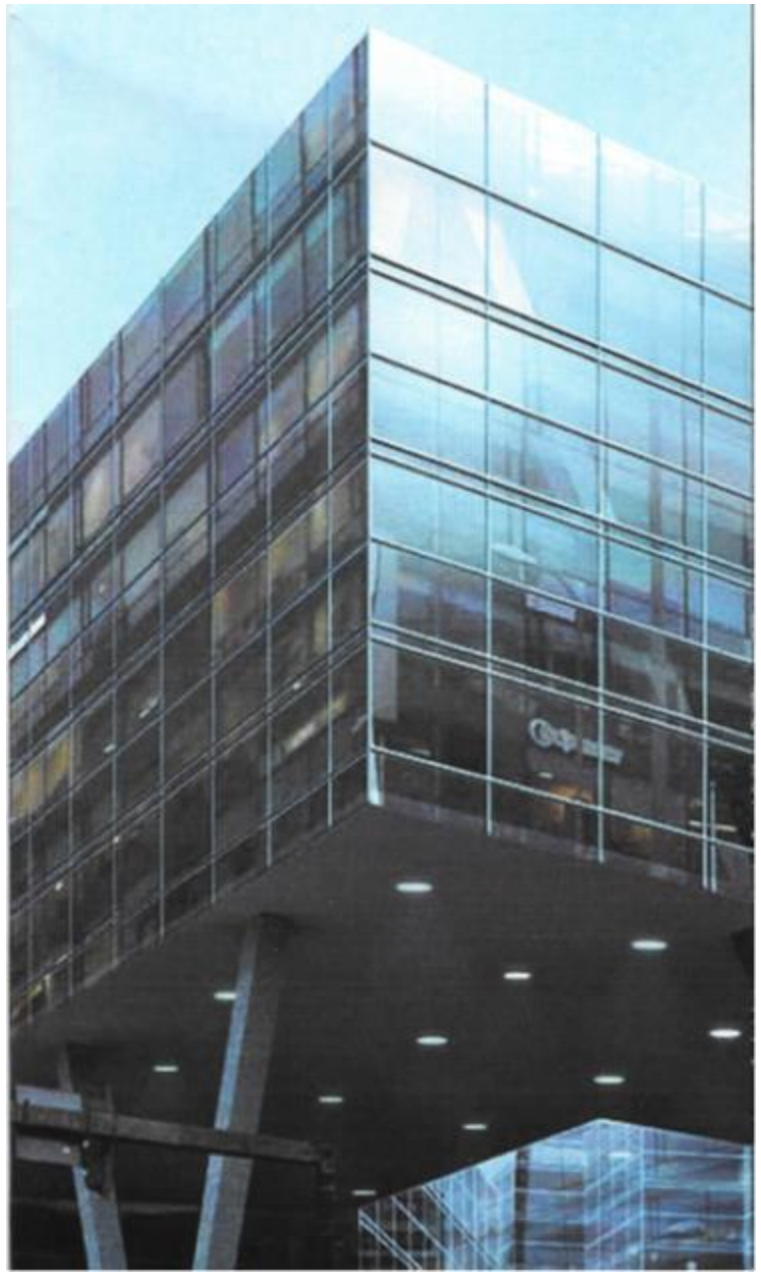


genecode drug discovery

ERADICATION OF HEPATITIS C VIRUS INFECTION WITH NOVEL ANTISENSE SEQUENCES

(Novel platform for highly efficient antisense compounds)

Biofit FOSTERING INNOVATION & TRANSFER
LILLE 2016 - FRANCE

BioFit Lille, November 2016

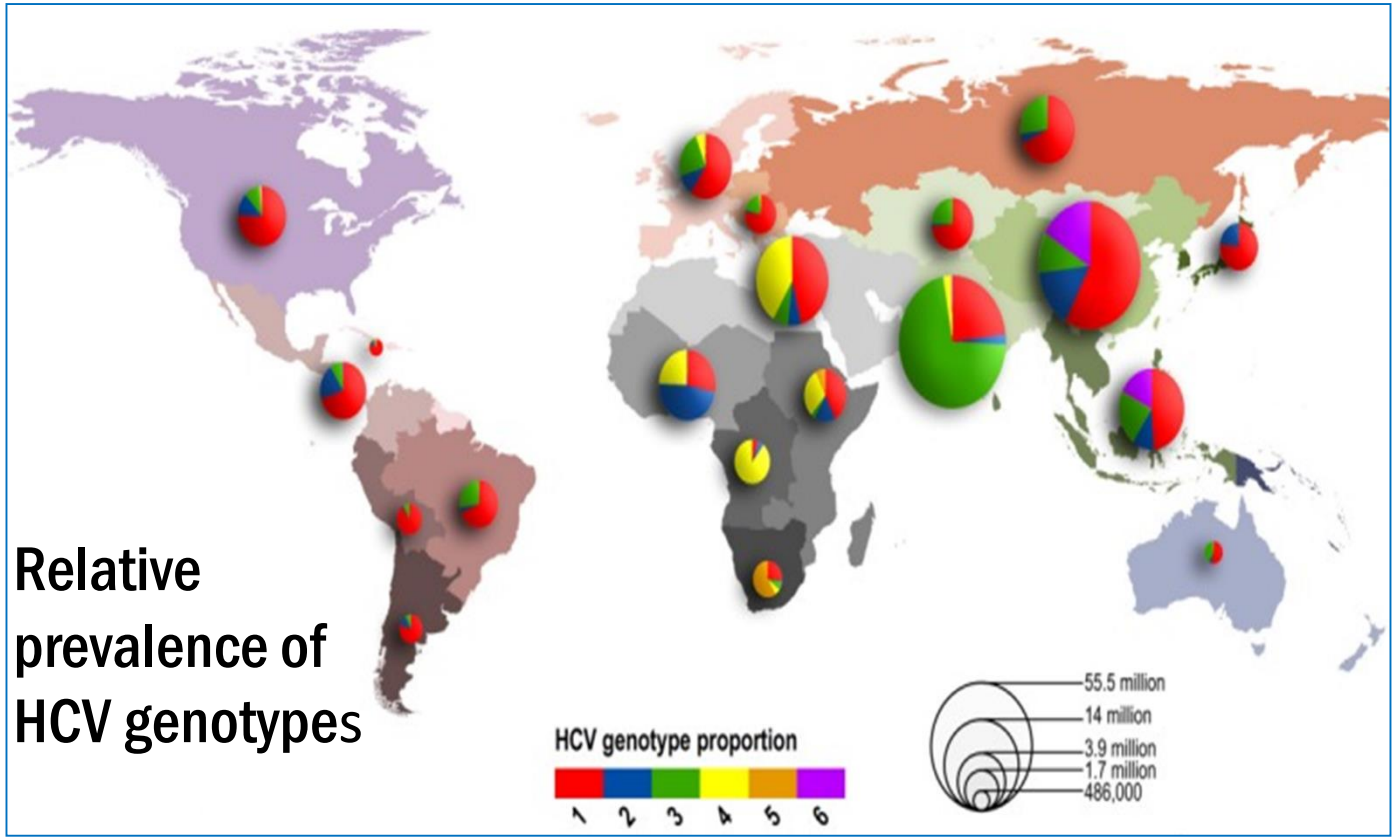
Hepatitis C virus (HCV) facts

- HCV causes chronic non-A non-B hepatitis.
- Chronic HCV patients eventually suffer from liver cirrhosis and liver cancer
- HCV is a single-stranded RNA-virus of around 10 kb.
- HCV has seven major genotypes.
- Recently, effective drugs have been developed and marketed to HCV-1b, primarily occurring in the US.
- All other HCV genotypes await effective treatment.

HCV challenge

CHRONIC HCV INFECTION

- Affects ~3% of the world's population.
- Leading cause of liver cirrhosis and carcinoma
- One of the key indications for liver transplantation
- Infected persons may infect others while not showing symptoms (yet)



Relative prevalence of HCV genotypes

Remaining challenges

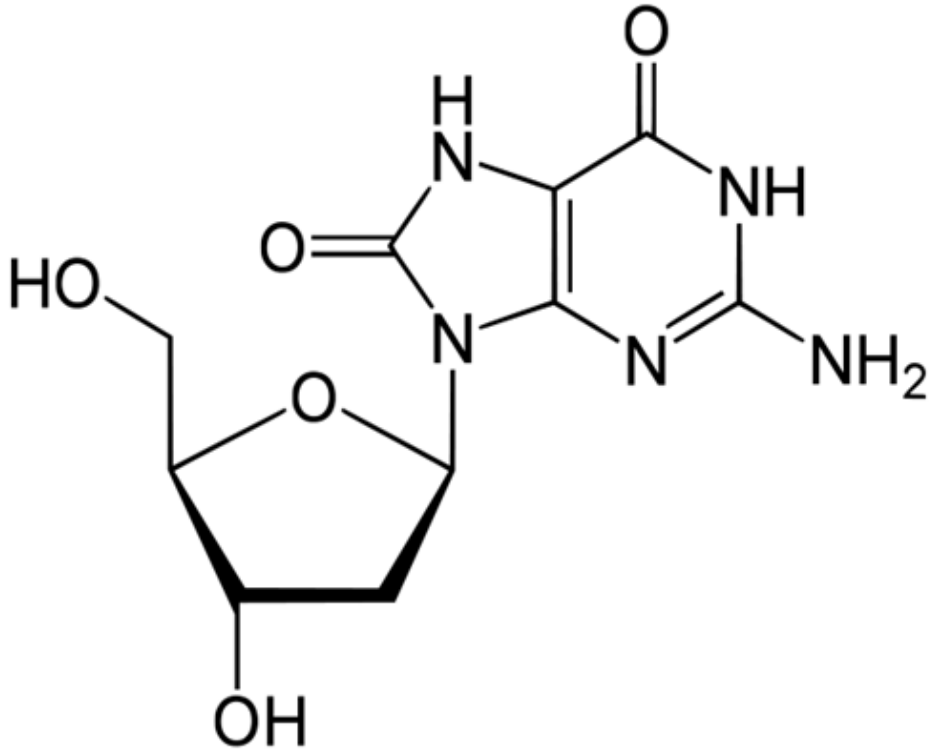
- Current HCV1b-treatment is based on oral drugs and is highly efficient.
- Current drugs do not readily treat other HCV-genotypes
- One antisense drug candidate, miravirsen (Santaris/GSK/Roche), was recenty put on hold despite good efficacy and excellent pharmacodynamics / kinetic properties in phase II clinical trials.

- Genecode has advanced it own antisense-stabilizing methods to develop effective treatment for HCV patients beyond HCV type 1.

Genecode innovation

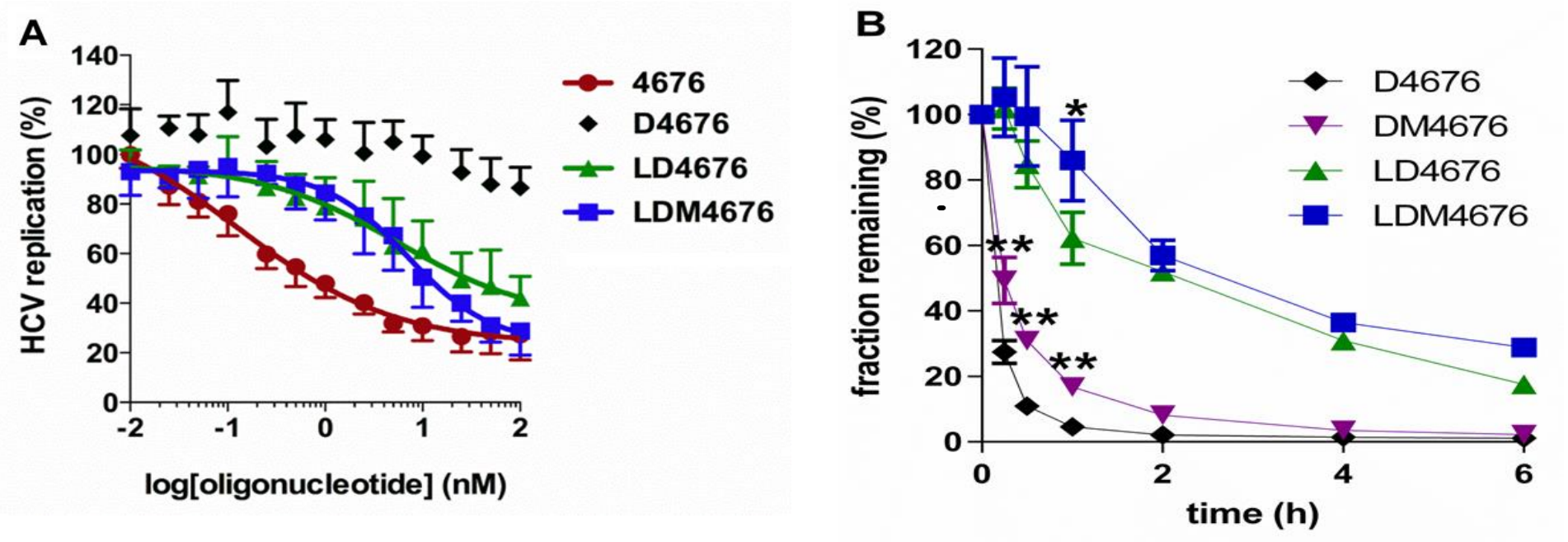
US Patent No 7.786.292 B2 "*Antisense agents combining strongly bounding base-modified oligonucloetide and artificial nuclease*" (August 31, 2010), European Patent No EP2013044 (August 29, 2012)

8-OXO-2'-DEOXYGUANOSINE (8-oxo-dG)



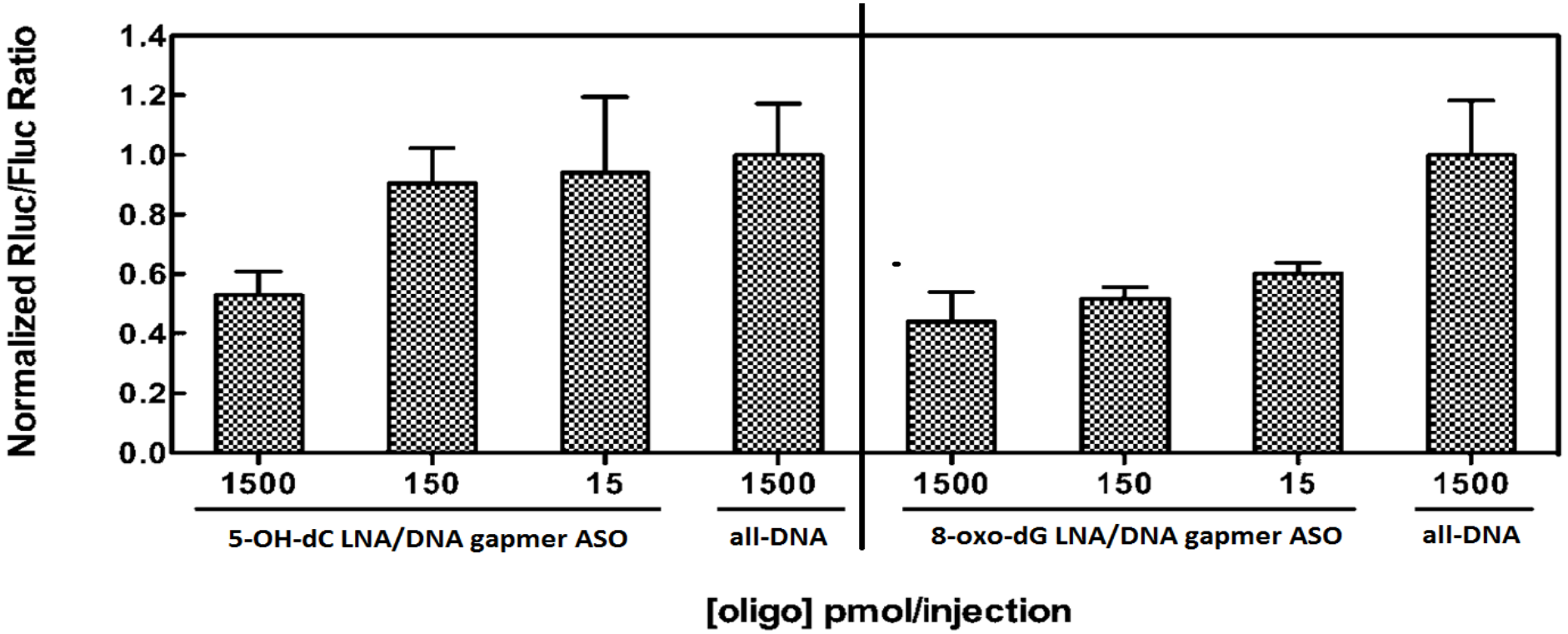
The specific binding of ASOs to the DNA or RNA targets can inactivate the replication, transcription, or translation of nucleic acids, thereby providing mechanism for controlling diseases such as cancer and viral infection. The binding of antisense oligonucleotide to a target can be thus used to alter gene expression, in variety of circumstances, e.g. to interfer with viral life cycles, or the growth of cancerous cells

8-oxo-dG residues allow more efficient inhibition of HCV replication in cell culture (A) and stabilize DNA and LNA/DNA gapmer ASOs in human serum (B)



4676 – isosequential siRNA (positive control); D4676 – all DNA oligonucleotide, DM4676 – all DNA ASO with three 8-oxo-dG residues, LD4676 – LNA/DNA gapmer, and LDM4676 – all DNA gapmer with three 8-oxo-dG residues.

8-oxo-dG (right) and to lesser extent also 5-OH-dC residues (left) inhibit expression of targeted marker gene in mouse liver



Plasmid expressing targeted Rluc and non-targeted Fluc markers was co-transfected with 1500 pmol of control all-DNA ASO, or with increasing amounts of modified LNA/DNA gapmer ASOs. Obtained Rluc/Fluc values were normalized to that in control animals (taken as 1).

GENECODE achievements and competitive advantages of GENECODE novel antisense technology

1. GENECODE modified ASOs can be used to target heavily structured RNAs such as coding region of HCV RNA genome.
2. 8-oxo-dG residues reduce the Tm of ASO:RNA duplexes.
3. 8-oxo-dG residues facilitate the cleavage of ASO:RNA duplexes by RNase H at multiple positions within the target region.
4. Incorporation of 8-oxo-dG residues increases stability of ASOs in serum.
5. Combination of these properties resulted in highly active ASOs functional both in *in vitro* system and in *in vivo* model.

Genecode team

Genecode management

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Piia Pilv, Chairman of the board
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Thank you

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