TELBIVUDINE, A POTENT AND SPECIFIC ANTI-HBV NUCLEOSIDE ANALOGUE: FROM the BENCH to its MARKETING APPROVALS (TYZEKA®, SEBIVO®)

- GENERAL CONSIDERATIONS
- LdT (TELBIVUDINE) REVISITED
- CLINICAL DEVELOPMENT of TELBIVUDINE (LdT)
- REGULATORY FILINGS and APPROVALS of TELBIVUDINE (LdT)
- CURRENT STATUS of TELBIVUDINE (TYZEKA®, SEBIVO®)
- CONCLUSIONS

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CNRS Research Director
Idenix Senior Scientist Fellow
Montpellier (France)

46th International Conference on Medicinal Chemistry (RICT 2010)
Reims (France), June 30 – July 02, 2010

GENERAL CONSIDERATIONS

★ **Nucleoside analogues and antiviral chemotherapy**

★ **Hepatitis B Virus (HBV) Infection :**

- ★ **World-wide significance**
- ★ **A blood-borne disease**
- ★ **Therapeutic treatments**

★ **The former (1971–2006) Laboratoire de Chimie Organique Biomoléculaire de Synthèse (UMR 5625 CNRS – Université Montpellier II) and its Laboratoire Coopératif Idenix - CNRS – Université Montpellier II (1999-2006)**

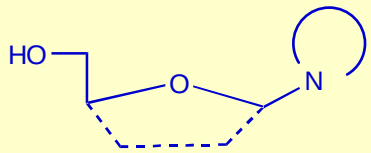
NUCLEOSIDE ANALOGUES and ANTIVIRAL CHEMOTHERAPY

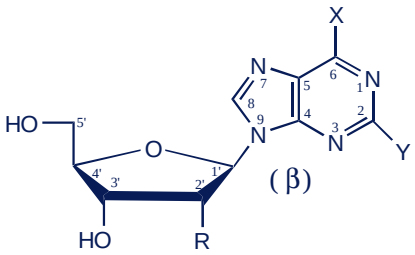
- **To date, more than fifty compounds have been approved by the Food and Drug Administration to be licensed as antiviral drugs**

- **About half of them:**

HAVE A NUCLEOSIDE STRUCTURE

NUCLEOSIDE ANALOGUES





NATURAL PURINE NUCLEOSIDES

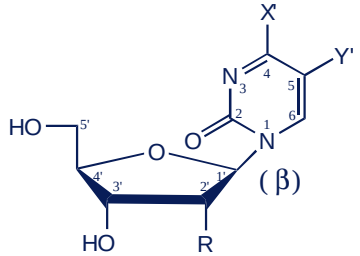
(X = NH_2, Y = H, R = H or OH)

(X = OH, Y = NH_2, R = H or OH)

MAIN BIOLOGICAL FUNCTIONS :

STRUCTURAL UNITS OF NUCLEIC ACIDS

(DNA, RNA)



NATURAL PYRIMIDINE NUCLEOSIDES

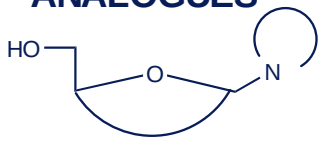
(X' = NH_2, Y' = H, R = H or OH)

(X' = OH, Y' = H, R = OH)

(X' = OH, Y' = CH_3, R = H)

MODIFICATIONS ON THE SUGAR AND/OR BASE MOIETY (TIES)

NUCLEOSIDE ANALOGUES



ANTIVIRAL ACTIVITIES

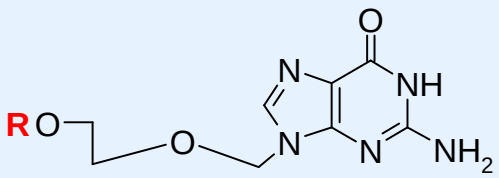
[mainly against viruses from the Herpesviridae family (HSV, VZV, CMV)

Vidarabine, (Val)acyclovir, famciclovir, (Val)ganciclovir, cidofovir

and against viruses from the Retroviridae family (HIV)

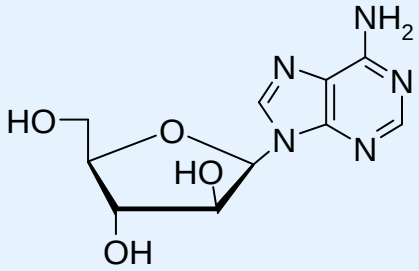
Zidovudine, stavudine, didanosine, zalcitabine, lamivudine and ziagen]

THREE ANTI-HERPES VIRUSES NUCLEOSIDE ANALOGUE DRUGS

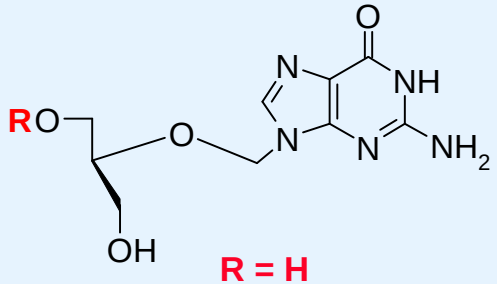


R = H,
9-(2-hydroxyethoxymethyl)guanine;
Acyclovir,ZOVIRAX
(*GlaxoSmithKline*)

R = L-Valyl
Acyclovir valinyl ester
Valacyclovir,VALTREX
(*GlaxoSmithKline*)



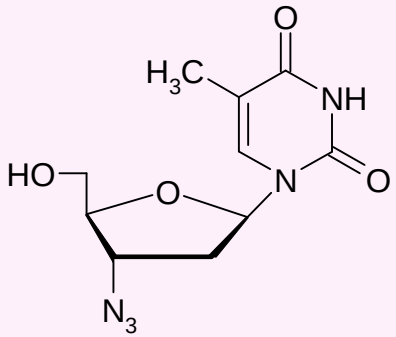
9-(arabinofuranosy)adenine
AraA, VIDARABINE
(*Parke Davis*)



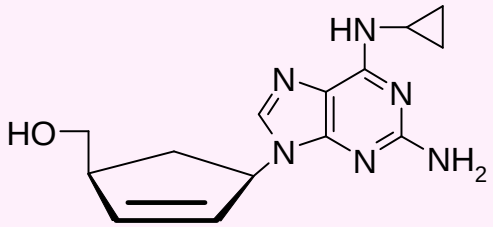
R = H
9-(1,3-dihydroxy-2-propoxymethyl) guanine; Ganciclovir,CYTOVENE
(*Hoffman-LaRoche Inc.*)

R = L-Valyl
Ganciclovir valinyl ester
Valganciclovir,VALCYTE
(*Hoffman-LaRoche Inc.*)

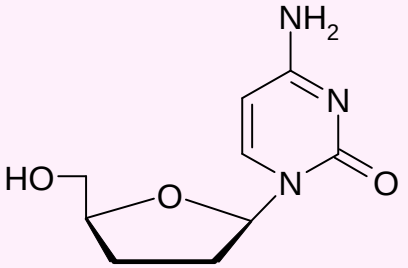
THREE ANTI-HIV NUCLEOSIDE ANALOGUE DRUGS



3'-azido-3'-deoxythymidine
AZT, Zidovudine, RETROVIR
(*GlaxoSmithKline*)

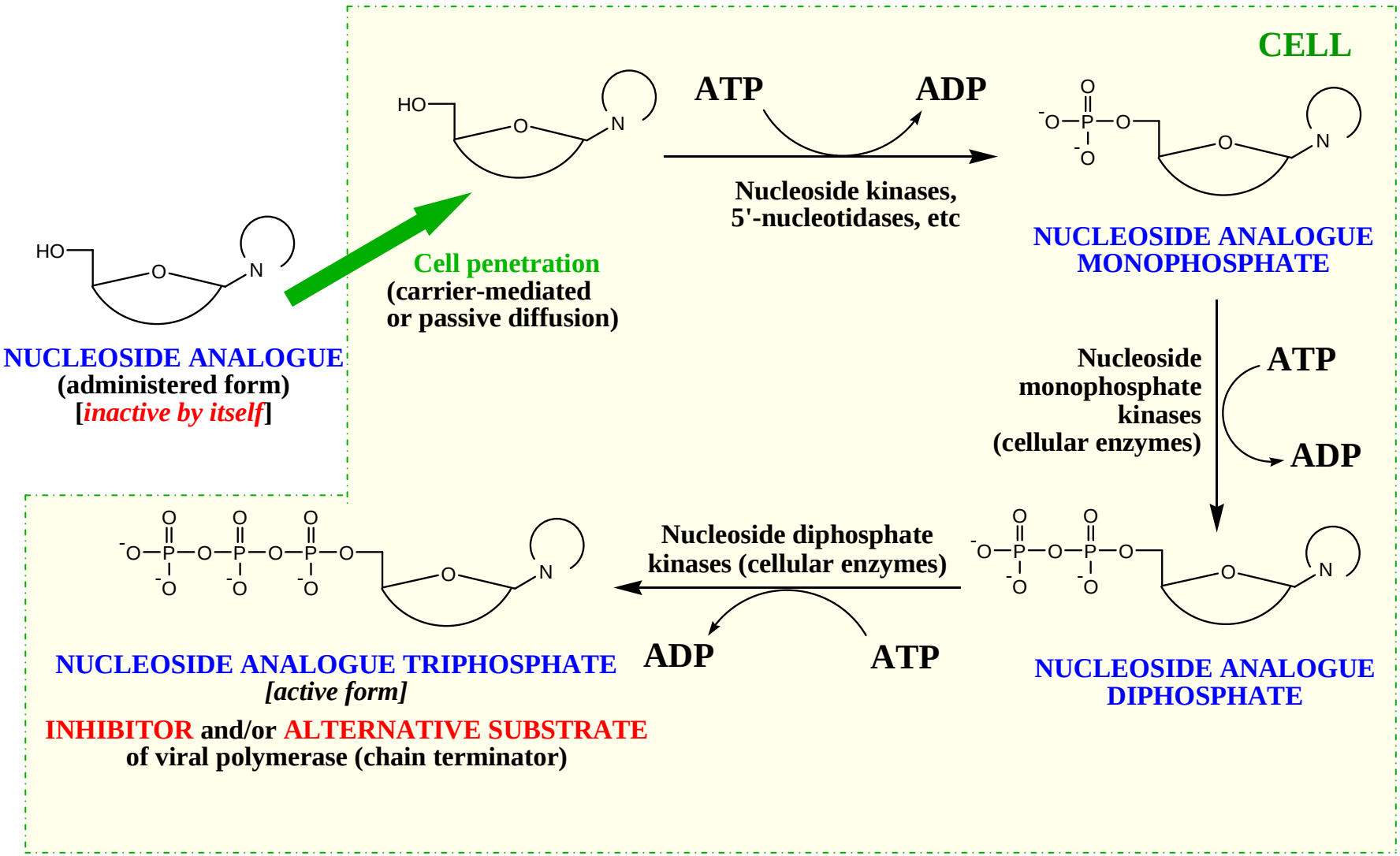


4-(2-amino-6(cyclopropylamino)-9H-purin-9-yl)-2-cyclopentene-1-methanol
Abacavir, ZIAGEN
(*GlaxoSmithKline*)



2',3'-dideoxycytidine
ddC, Zalcitabine,HIVID
(*Hoffman-LaRoche Inc.*)

MODE OF ACTION OF ANTIVIRAL NUCLEOSIDE ANALOGUES



NUCLEOSIDE ANALOGUES and ANTIVIRAL CHEMOTHERAPY

CURRENTLY

Intense research efforts are devoted

to finding new nucleoside analogues,

not only active against herpes viruses and HIV
(*but with less side effects than the drugs currently in use*)

but also effective against other virus families
(*Hepadnaviridae, Flaviviridae, Filoviridae, Arenaviridae, etc*)

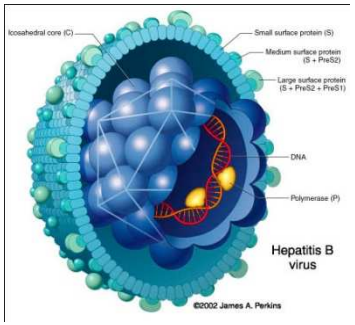
involved in severe human diseases

(*hepatitis, hemorrhagic fevers, respiratory diseases*)

EXAMPLE of a SEVERE VIRAL HUMAN DISEASE

HEPATITIS B VIRUS (HBV) INFECTION

World-wide significance :



- **Over 2 billion (2000 million) people infected worldwide**
- **Around 350 million are chronic carriers**
- **At least 1 million chronically infected individuals die each year**

A typically blood-borne disease :

- **Very High viral loads (from 10^6 to 10^{11} virions/ml of blood in chronic carriers)**
- **Very Low minimum required volume of blood to transmit HBV infection (0.00004 ml = 0.04 µl)**
- **High risk of infection following needlestick injury with positive HBV patient (7-30%)**

HEPATITIS B VIRUS (HBV) INFECTION

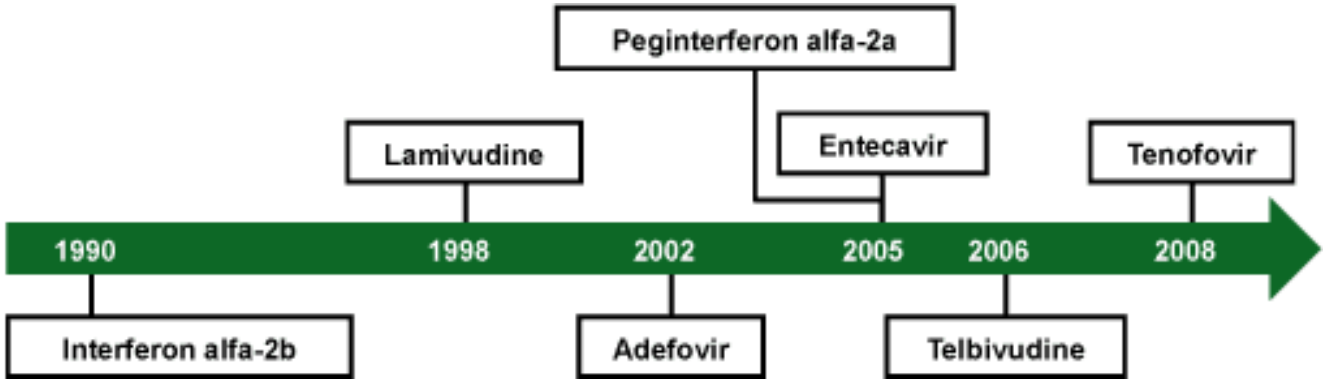
• Prevention:

Safe and effective anti-HBV vaccines are available

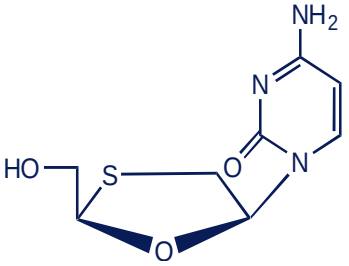
However: Several million people are still being newly infected annually

• Major therapies:

Currently, Interferon α-2b and Peginterferon α-2a,
three nucleoside analogues (Lamivudine, Entecavir, Telbivudine)
and two nucleotide analogues (Adefovir and Tenofovir)
are approved by the FDA for the treatment of chronic HBV infection



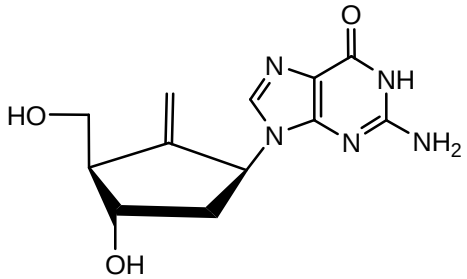
APPROVED ANTI-HBV NUCLEOSIDE ANALOGUES



LAMIVUDINE
[Epivir, 3TC]
(*Glaxo Wellcome PLC and Biochem Pharma Inc.*)
Approvals : 1995 HIV; 1998 HBV

⇩

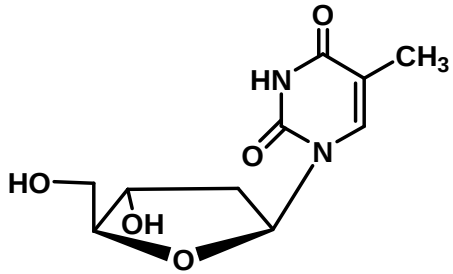
L-enantiomer dideoxycytidine analogue



ENTECAVIR
[Baraclude]
(*Bristol-Myers Squibb*)
Approval : 2005 HBV

⇩

D-enantiomer carbocyclic 2'-deoxyguanosine analogue

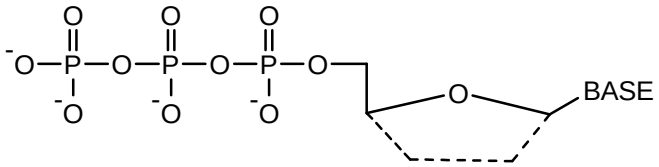


TELBIVUDINE
[Tyzeka, Sebivo, L-dT]
(*Idenix Pharmaceuticals and Novartis*)
Approvals : 2006 and 2007 HBV

⇩

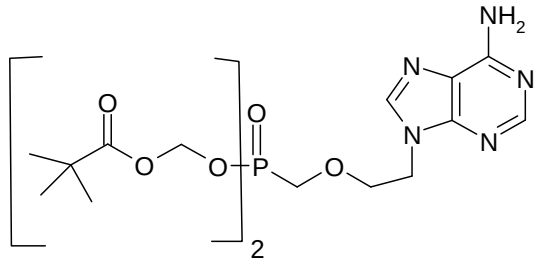
L-enantiomer 2'-deoxythymidine analogue

Intracellular di- and tri-phosphorylations

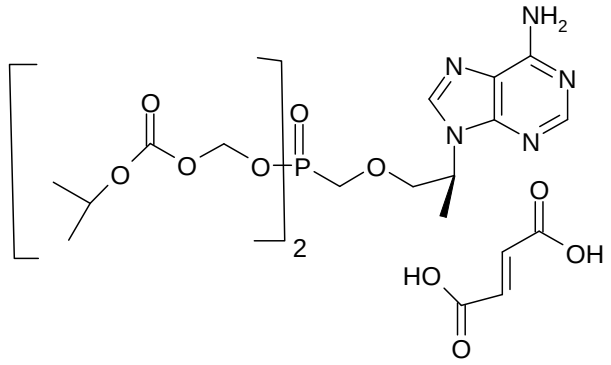


NUCLEOSIDE ANALOGUE TRIPHOSPHATE
[active form]

APPROVED ANTI-HBV NUCLEOTIDE ANALOGUES

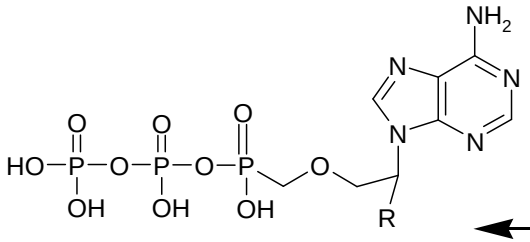


ADEFOVIR DIPIVOXYL
[Hepsera, Bis(POM)PMEA] (*Gilead*)
Approval : 2002 HBV
Acyclic phosphonate diester dideoxyadenosine analogue (Prodrug)



TENOFOVIR DISOPROXIL FUMARATE
[Viread, Bis(POC)PMPA] (*Gilead*)
Approvals : 2001 HIV; 2008 HBV
Acyclic phosphonate diester dideoxyadenosine analogue (Prodrug)

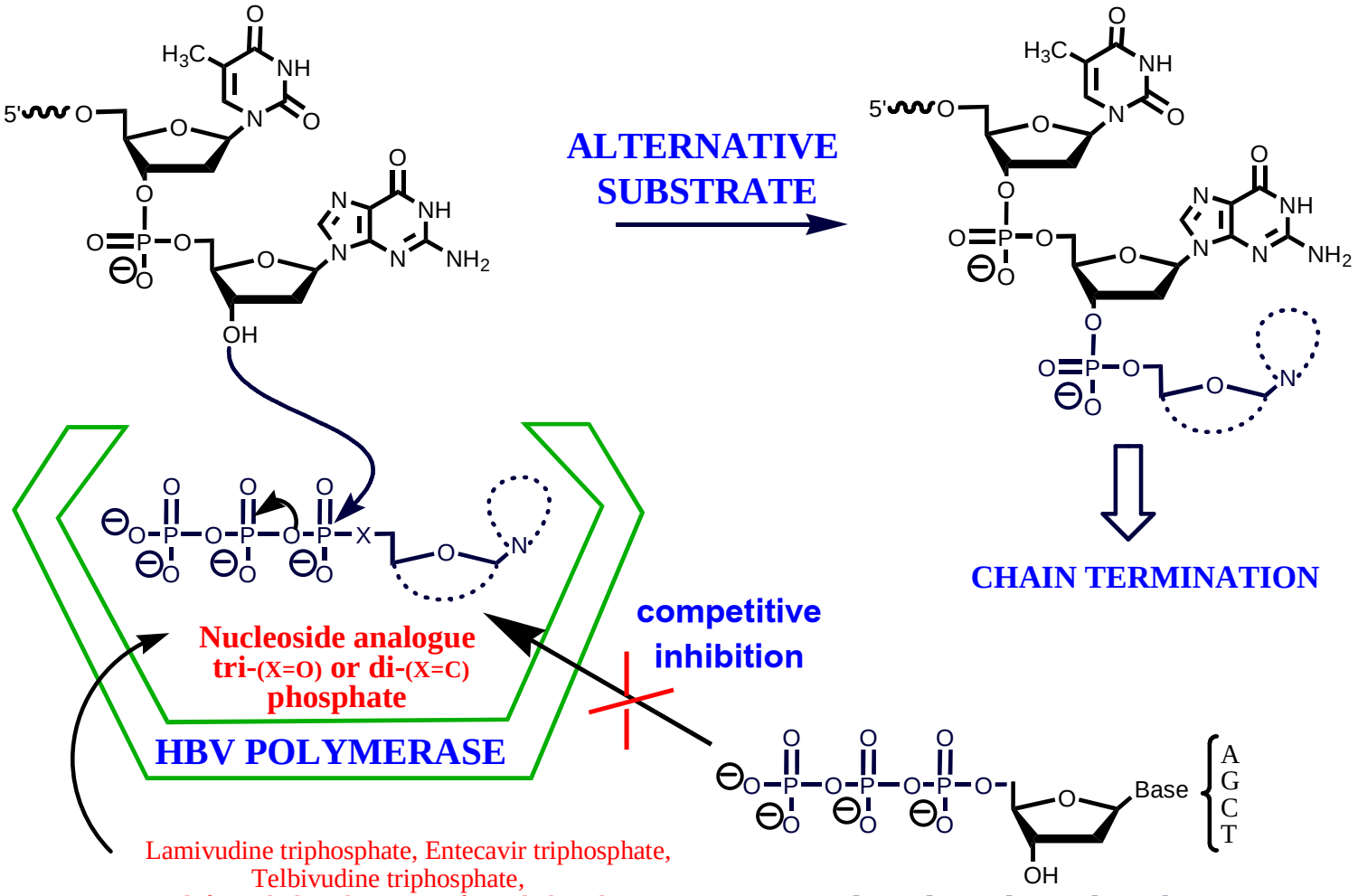
Intracellular esterase activity, then kinase mono- and di-phosphorylation



NUCLEOSIDE PHOSPHONATE ANALOGUE DIPHOSPHATE
[active form]

MODE OF ACTION OF ANTI-HBV NUCLEOTIDE ANALOGUES

Orally-bioavailable drugs, which are converted intracellularly into their active tri- or di-phosphate form



GENERAL CONSIDERATIONS (end)

THE FORMER

UMR 5625 CNRS – UNIVERSITE MONTPELLIER II

Laboratoire de Chimie Organique Biomoléculaire de Synthèse

(1971 – 2006)

and its

LABORATOIRE COOPERATIF:

Idenix (formerly Novirio) – CNRS – Université Montpellier II

(1999 – 2006)

LABORATOIRE DE CHIMIE ORGANIQUE BIOMOLECULAIRE DE SYNTHESE

CNRS - Unité Mixte de Recherche 5625 - Université Montpellier II

Site web : http://lcobs.univ-montp2.fr

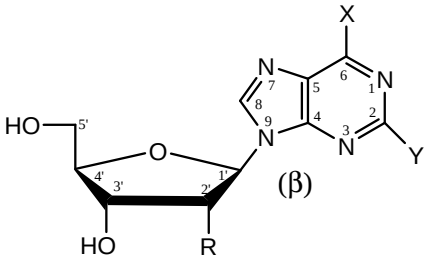
[Established (1971) and firstly headed by Prof. J.-L. Imbach (→ 1998). then headed by Dr G. Gosselin (1999-2006)]

Several Set of Research Themes, including:

► **Modified Oligonucleotides** *(Dr. Bernard Rayner Group)*

► **Nucleoside Analogues** *(Dr. Gilles Gosselin Group)*

Synthesis and Study of Nucleoside Analogues as Potential Antiviral and/or Antitumor Agents



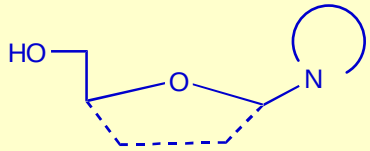
NATURAL PURINE NUCLEOSIDES

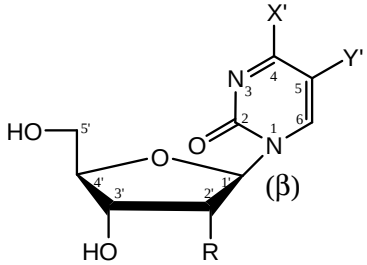
(X = NH_2, Y = H, R = H or OH)

(X = OH, Y = NH_2, R = H or OH)

MODIFICATIONS ON THE SUGAR AND/OR BASE MOIETY (TIES)

NUCLEOSIDE ANALOGUES





NATURAL PYRIMIDINE NUCLEOSIDES

(X' = NH_2, Y' = H, R = H or OH)

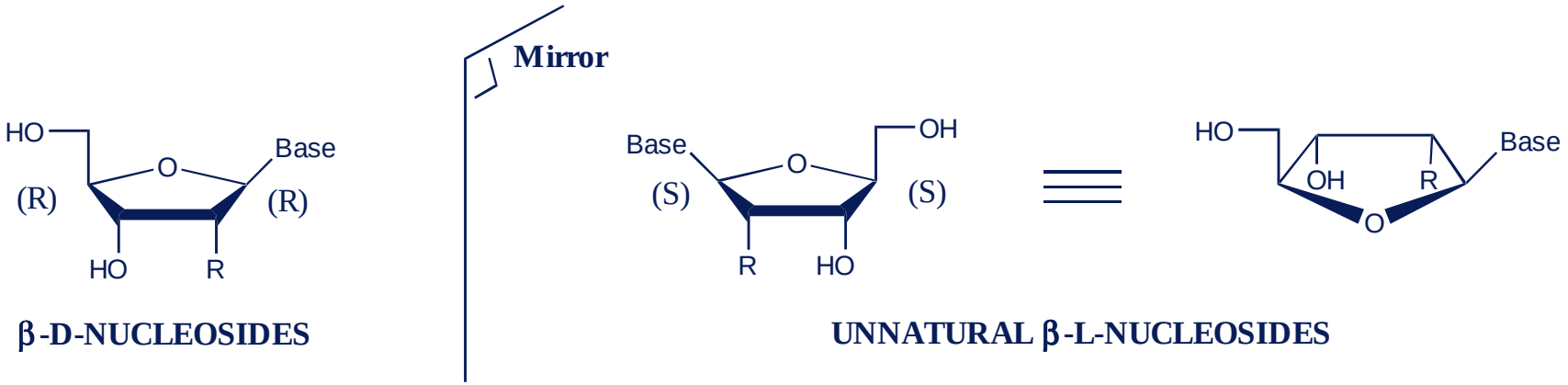
(X' = OH, Y' = H, R = OH)

(X' = OH, Y' = CH_3, R = H)

Starting in the 1990's

► **Nucleoside Analogues** *(Dr. Gilles Gosselin Group)*

Synthesis and Study of New Nucleoside Analogues Endowed with the Unnatural β-L-configuration

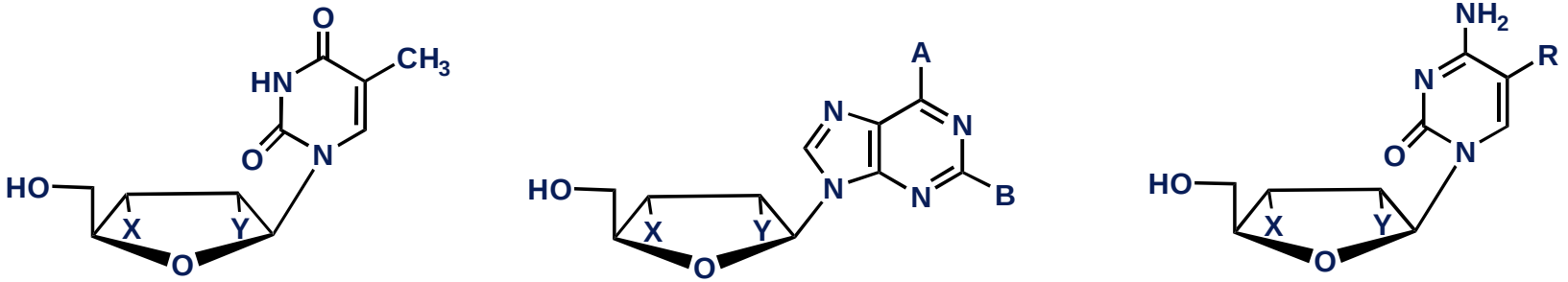


β-D-NUCLEOSIDES

UNNATURAL β-L-NUCLEOSIDES

Starting in the 1990's

Synthesis and Study of Numerous New Nucleoside Analogues Endowed with the Unnatural β-L-configuration



(X, Y = H, OH, N_3, NH_2, F, double bond; A, B = H, NR_1R_2, OR_3, SR_3; R = H, halogen, alkyl; etc., etc. …)

From antiviral evaluations in cell culture experiments

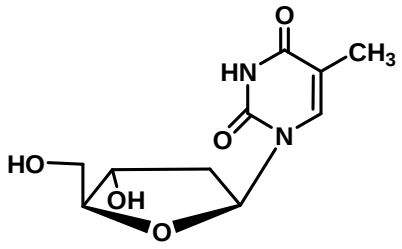
- Dr. Anne-Marie Aubertin (*Strasbourg*) [HIV],
- Prof. Erik De Clercq (*Leuven, Belgium*) [broad range of viruses],
- Prof. Jean-Pierre Sommadossi (*Birmingham, Alabama*) [HBV]

a Structure-Activity Relationship was established:

Nucleoside analogues belonging to the β-L-2'-deoxyribofuranosyl series (X = OH; Y = H) are endowed with a unique specificity for anti-HBV activity

1997: Discovery that nucleosides from the β-L-2'-deoxyribofuranosyl series are endowed, in cell culture experiments, with a unique specificity for anti-HBV activity

Furthermore, among these β-L-2'-deoxyribofuranonucleosides



LdT

was one of the most potent, selective and specific inhibitors of HBV replication

- **File on August 10, 1998 a provisional patent application** (US 60/096, 110) entitled « β-L-2'-Deoxy-Nucleosides for the Treatment of Hepatitis B Virus » which was issued as WO 00/009531 on Feb 24, 2000 with G. Gosselin, J.-L. Imbach and M.L. Bryant as inventors, and assigned to CNRS (France) and Novirio (currently Idenix)

- **Establish on January 01, 1999 the Laboratoire Coopératif Idenix (formerly Novirio) - CNRS – Université Montpellier II inside the UMR 5625 CNRS – Université Montpellier II**

- **Selected LdT (TELBIVUDINE) as a highly attractive preclinical development candidate for the treatment of chronic HBV infection**

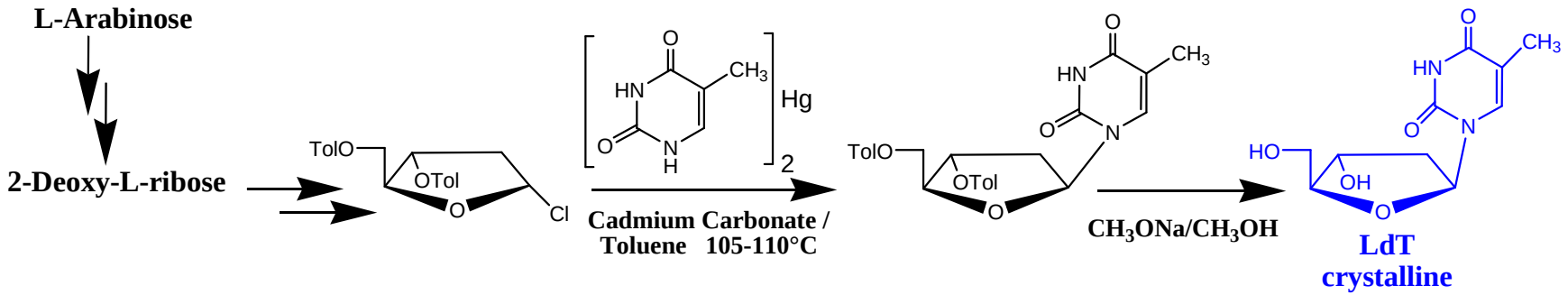
LdT (TELBIVUDINE) REVISITED

- ★ **First LdT reported synthesis (1964, Prague)**
- ★ **Other reported data (1964 → 1997)**
- ★ **Montpellier LdT syntheses:**
  - ❖ **First synthetic approach (1990)**
  - ❖ **Subsequent semi-large scale syntheses (1999)**
- ★ **Intracellular activation (Metabolism and Pharmacology)**
- ★ **Preclinical studies in animal models:**
  - ❖ **Anti-HBV activity (woodchuck)**
  - ❖ **Pharmacological studies (woodchuck, cynomologus monkey, etc.)**

LdT: PREVIOUSLY REPORTED LITERATURE DATA

1964: LdT, FIRST LITERATURE EXAMPLE of an L-NUCLEOSIDE

[J. Smejkal and F. Sorm, *Collect. Czech. Chem. Commun*. 29, 2809 (1964)]



SUBSEQUENT (1964 → 1997) LITERATURE DATA ON LdT:

- **Other Syntheses:** A. Holy, *Collect. Czech. Chem. Commun*. 37, 4072 (1972); C.B. Reese and Y.S. Sanghvi, *J. Chem. Soc. Chem. Commun*. 877 (1983); S. Fujimori et al., *Nucleosides & Nucleotides* 11, 341 (1992)
- **Biochemical and biological studies :** M. Jurovcik and A. Holy, *Nucleic Acids Res*. 3, 2143 (1976); A. Holy et al., *Biol. Chem. Hoppe-Seyler*, 366, 355 (1985); S. Spadari et al., *J. Med. Chem*. 35, 4214 (1992); G. Maga et al., *Biochem. J.* 294, 381 (1993) and 302, 279 (1994); A. Verri et al. *Biochem. J*. 328, 317 (1997)
- **LdT 5'-triphosphate :** T. Yamaguchi et al., *Nucleic Acids Symposium Series* 9, 135 (1993); T. Yamaguchi et al., *Biochem. Bioph. Res. Commun*. 200, 1023 (1994); F. Focher et al., *Nucleic Acids Res*. 23, 2840 (1995); D.G. Semizarov et al., *J. Biol. Chem*. 272, 9556 (1997)

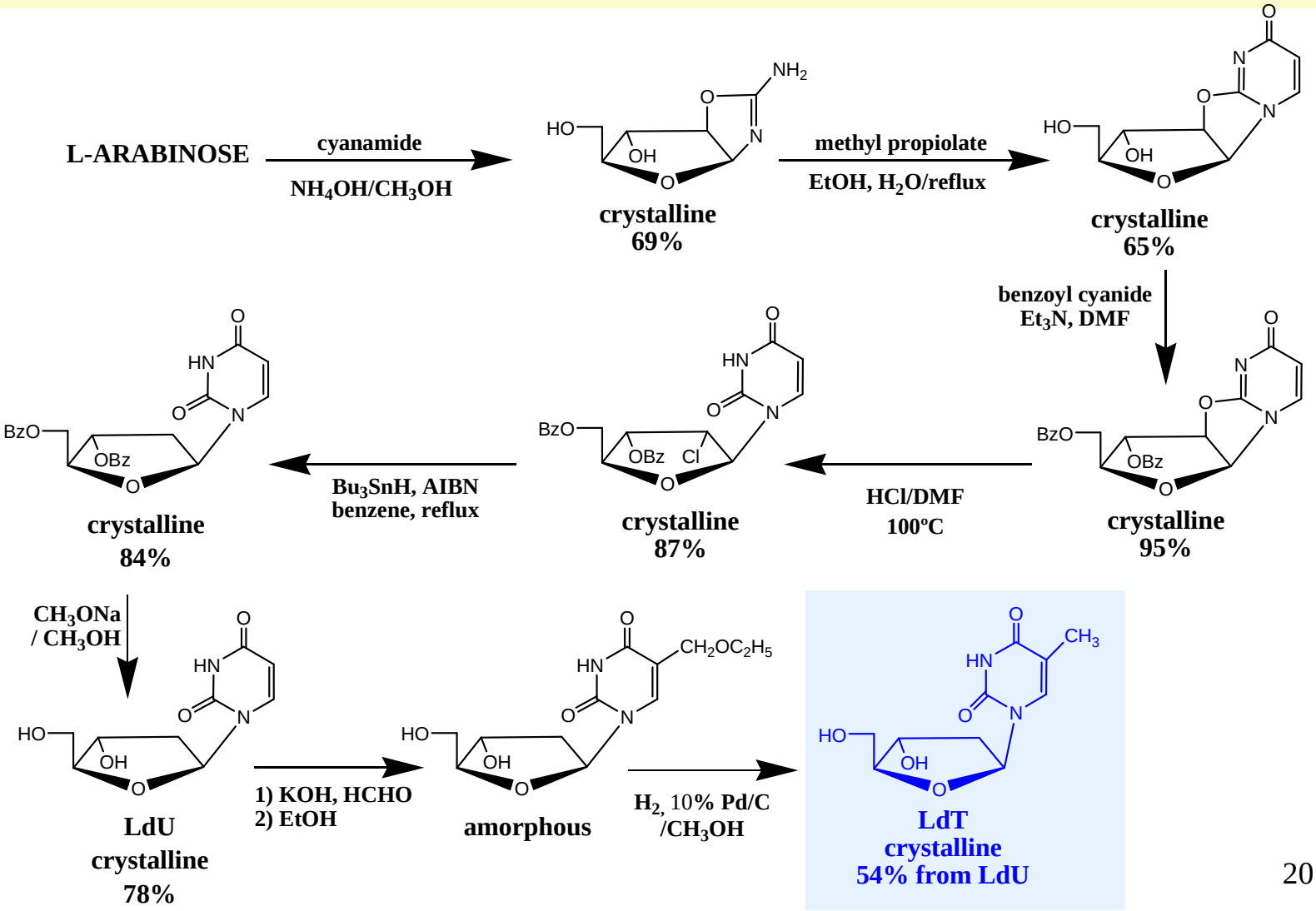
NONE OF THESE STUDIES DEALING WITH HBV

1990 : MONTPELLIER LdT SYNTHETIC APPROACH

(*as a monomer for the synthesis and study of modified oligonucleotides*)

F. Morvan, C. Genu, B. Rayner, G. Gosselin, J.-L. Imbach, *Biochem. Res. Commun*. 172, 537 (1990)

[similar procedure as that previously reported by A. Holy, *Collect. Czech. Chem. Commun*. 37, 4072 (1972)]



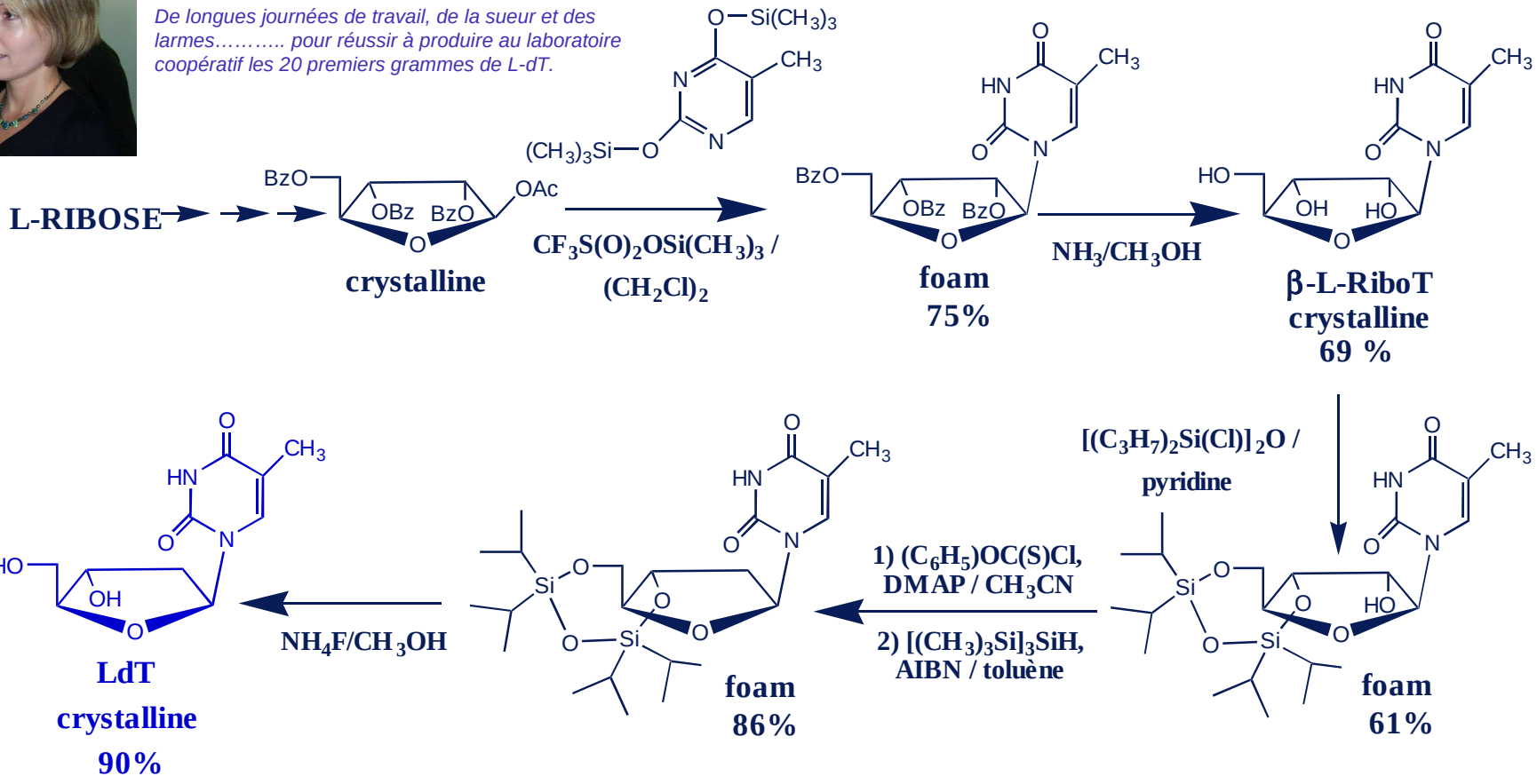
1999: MONTPELLIER TELBIVUDINE SEMI-LARGE SCALE (20g) SYNTHESIS

(Laboratoire Coopératif Idenix (formerly Novirio) – CNRS – Université Montpellier II)

C. Pierra, D. Dukhan, … , J.-P. Sommadossi, G. Gosselin, *Antiviral Res*. 46 (1), A62 (2000)

C. Pierra, G. Gosselin, … , J.-P. Sommadossi, *Current Protocols in Nucleic Acids*, Suppl. 24, 14.3 (2006)

De longues journées de travail, de la sueur et des larmes……. pour réussir à produire au laboratoire coopératif les 20 premiers grammes de L-dT.

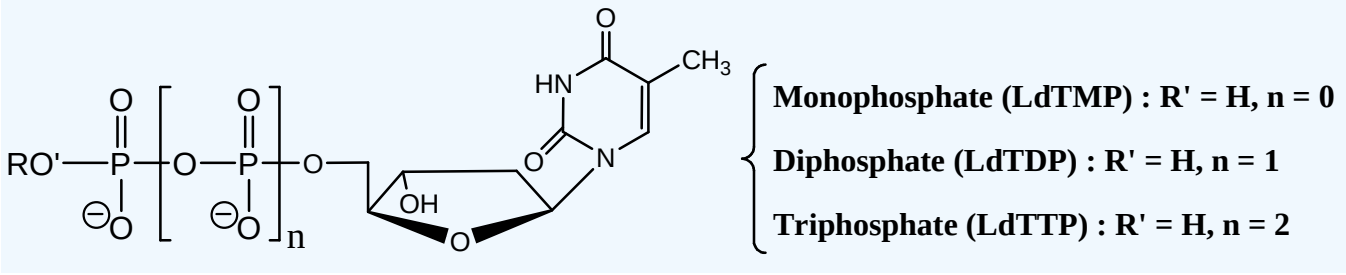


PHARMACOLOGY OF LdT (1)

B. Hernandez-Santiago, … G. Gosselin, … J.-P. Sommadossi,
***Antimicrob. Agents Chemother*. 46, 1728 (2002)**

Intracellular concentrations of metabolites detected in Hep-G2 cells and hepatocytes after 24 hr of incubation with 10 µM of [^{3}H]LdT

Structure of the detected metabolites :



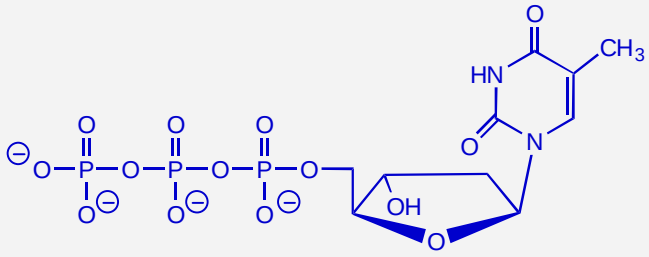
	Intracellular concentration (pmol / 10^6 cells)		
	LdTMP	LdTDP	LdTTP
Hep-G2 cells	8.1	2.9	27.7
Primary hepatocytes (isolated from human liver)	15.2	2.5	16.5

LdT is rapidly and extensively converted into its 5'-triphosphate derivative

PHARMACOLOGY OF LdT (2)

B. Hernandez-Santiago, … G. Gosselin, … J.-P. Sommadossi,
***Antimicrob. Agents Chemother*. 46, 1728 (2002)**

STUDY OF LdT 5'-TRIPHOSPHATE

	 **LdTTP**
IC_{50} (µM) cellular DNA polymerases (α, β, γ)	> 100
IC_{50} (µM) woodchuck HBV DNA polymerase	0.24
Intracellular Half-life	≥ 15h*
Concentration : 24h after removal of the parent drug LdT from the cell	7.4 pmol/10^6 cells**

*** This long half-life and ** intracellular persistence indicate that LdTTP concentration remains above the EC_{50} for HBV in 2.2.15 cells for 24 h (Predictive of once daily dosing)**

PRECLINICAL STUDIES IN ANIMAL MODELS (1):
Activity and Safety of LdT in chronically HBV infected woodchucks

M. L. Bryant, … G. Gosselin, … J.-P. Sommadossi,
***Nucleosides, Nucleotides & Nucleic Acids*, 20, 597 (2001)**

When LdT was given orally
once daily at 10mg/kg/day during 4 weeks :

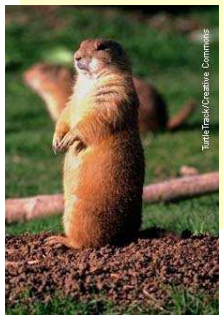
Serum woodchuck hepatitis virus DNA levels (*HBV viremia*)
decreased up to 8 logs in the treated animals

[At the same dose, lamivudine (3TC) used for comparison reduced the woodchuck hepatitis virus DNA level in serum by 0.5 logs]

LdT was well tolerated and caused no drug-related toxicity through 4 weeks of treatment and 4 weeks of follow-up

PRECLINICAL STUDIES IN ANIMAL MODELS (2):

Pharmacological Studies



D. N. Standring, … G. Gosselin, … J.-P. Sommadossi,
Antiviral Chem. Chemother. 12 (Supp.1), 119 (2001)

ABSOLUTE ORAL BIOAVAILABILITY (%F) =

😐 **in woodchucks : 38%** ☺ **in cynomologus monkeys : 69%**

(Renal clearance appeared to be the major pathway of LdT éliminations)

FURTHERMORE

(other animal models)

E. G. Bridges, J. R. Selden, S. Luo, *Antimicrobial Agents Chemotherapy*, **52** (7), 2521 – 2528 (2008)

- ☺ **No effect of LdT on physiology of rats or cynomologus monkeys at doses up to 500 mg/kg/day, treated for 6 or 9 months respectively**
- ☺ **No evidence of carcinogenicity in rats or transgenic mice at LdT doses up to 2000 mg/kg/day, treated for 2 years or 6 months respectively**
- ☺ **No effect on reproductive fertility in rats at doses up to 2000 mg/kg/day**
- ☺ **No effect of LdT on fetal or postnatal development in rats or rabbits at doses up to 1000 mg/kg/day**

LdT (telbivudine) REVISITED

SUMMARY

***From the discovery of LdT anti-HBV activity* (1997)**
***to its preclinical development* (1999-2002)**

G. Gosselin, C. Pierra, ..and J.-P. Sommadossi, In *Frontiers in Nucleosides and Nucleic Acids*
R.F. Schinazi & D.C. Liotta eds, IHL Press (Tucker, USA), pp 309-318 (2004)

Owing to its antiviral potency and to its specific and selective profile, LdT (TELBIVUDINE) appeared as an *highly attractive clinical development candidate* for the treatment of chronic HBV infection

TELBIVUDINE (LdT) DEVELOPMENT

Idenix LABORATOIRES
http://www.idenix.com

NOVARTIS
http://www.novartis.com

Idenix developed LdT (telbivudine) in collaboration with Novartis Pharma AG under a development and commercialization agreement established in May 2003

★ Clinical Phases I/II and IIb

CLINICAL PHASE I/II: « A Dose-Finding Study of Once-Daily Oral Telbivudine in HBeAg-Positive Patients With Chronic Hepatitis B Virus Infection », C.-L. Lai, S. G. Lim, N. A. Brown, X.-J. Zhou, D. M. Llyod, Y.-M. Lee, M.-F. Yuen, G. C. Chao and M. W. Myers, *Hepatology* 2004; 40, 719-726.

CLINICAL PHASE IIb: « A 1-Year Trial of Telbivudine, Lamivudine, and the Combination in Patients With Hepatitis B e Antigen-Positive Chronic Hepatitis B », C.-L. Lai, N. Leung, E.-K. Teo, M. Tong, F. Xong, H.-W. Hann, S. Han, T. Poynard, M. Myers, G. Chao, D. M. Llyod, and the Telbivudine Phase II Investigator Group, *Gastroenterology* 2005; 129, 528-536.

Results after 1 year supported antiviral superiority of LdT over lamivudine (3TC)

For reviews, see :

- «Telbivudine : A New Nucleoside Analogue for the treatment of Chronic Hepatitis B», S.-H. B. Han. *Expert Opin. Investig, Drugs*, 14, 511-519 (2005);
- «Telbivudine : A Novel Nucleoside Analog for Chronic Hepatitis B», J.W. Kim, S.H. Park and S.G. Louie. *The Annals of Pharmacotherapy*, 40, 472-478 (2006)

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http://www.idenix.com

TELBIVUDINE (LdT) DEVELOPMENT

NOVARTIS
http://www.novartis.com

★ International phase III: the GLOBE study

Enrolled 1,367 patients from approximately 135 clinical centers

- Both HBeAg positive and HBeAg negative patients enrolled
- Patients receive LdT 600 mg/day or lamivudine (3TC) 100 mg/day

Efficacy and safety of LdT after one year:

C.-L. Lai, …, N. A. Brown, and the Globe Study Group, *N. Engl. J. Med.*, 357 (25), 2576-2588 (2007)

- ☺ High degree of efficacy on all virologic and clinical endpoints
- ☺ Significantly greater reduction of serum HBV DNA vs. lamivudine
- ☺ More LdT patients with HBV DNA non-detectable by Polymerase Chain Reaction (PCR) assay
- ☺ Greater improvement of liver histology with LdT in HBeAg positive patients
- ☺ Significantly less resistance with LdT
- ☺ Favorable safety and tolerability profile

Final (two-year) results:

J. Rasenack, …, N. A. Brown, *Journal of Hepatology* Vol. 46 (Suppl. 1), 681A (2007)
S. Zeuzem, …, K. Galil, *Hepatology* Vol. 46 (N°4, Suppl. 1), S195 (2007)
Y.-F. Liaw, …, The GLOBE Study Group, *Gastroenterology* Vol. 136, Issue 2, 486-495 (2009)

☺ **The results confirmed those obtained after one year and defined patient characteristics associated with optimal responses to telbivudine, contributing to on-treatment patient management strategies**

For a review, see :

«Telbivudine for chronic hepatitis B: the GLOBE trial » : M.-F. Yuen & C.-L. Lai, *Future Virology*, 3 (4), 317-323 (2008)

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TELBIVUDINE (LdT) DEVELOPMENT

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★ FURTHER STUDIES (1)

- «Absence of Food Effect on the Pharmacokinetics of Telbivudine Following Oral Administration in Healthy Subjects» X.-J. Zhou, …. & N. A. Brown, *J. Clin. Pharmacol.* Vol. 46, 275-281 (2006)

- «Treatment of Hepatitis B e Antigen-Positive Chronic Hepatitis with Telbivudine or Adefovir» H. L. Y. Chan, …, N. A. Brown & the 108 Study Group, *Ann. Intern. Med.*, 147 (11), 745-754 (2007)

One-Year Results of an International clinical trial comparing LdT and adefovir dipivoxyl:

(***Enrolled 135 HBeAg positive patients who received LdT 600 mg/day or adefovir dipivoxyl 10 mg/day***)

Greater reductions in viral load both in patients who received telbivudine for 52 weeks *(-6.55 $\log_{10}$ copies/mL)* ***and in those who were switched to telbivudine after 24 weeks of adefovir treatment*** *(-6.44 $\log_{10}$ copies/mL)* ***compared with those patients treated with adefovir for 52 weeks*** *(-5.72 $\log_{10}$ copies/mL)*

- «Pharmacokinetics of Telbivudine in Subjects with Various Degrees of Renal Impairment» X.-J. Zhou, …. & N. A. Brown, *Antimicrobial Agents and Chemotherapy*, Vol. 51 (12), 4231-4235 (2007)

- «Telbivudine Versus Lamivudine in Chinese Patients with Chronic Hepatitis B: Results at 1 Year of a Randomized, Double-Blind Trial» J. Hou, …. & J. Jia, *Hepatology*, Vol. 47 (2), 447-454 (2008)

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TELBIVUDINE (LdT) DEVELOPMENT

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http://www.novartis.com

★ FURTHER STUDIES (2)

- «Telbivudine, a nucleoside analog inhibitor of HBV polymerase, has a different in vitro cross-resistance profile than the nucleoside analog inhibitors adefovir and tenofovir» M. Seifer, ….. & D. N. Standring, *Antiviral Research*, Vol. 81 (2), 147-155 (2009)

- «Population Pharmacokinetics of Telbivudine and Determination of Dose Adjustment for Patients With Renal Impairment» X.-J. Zhou, …. & H. S. Pentikis, *J. Clin. Pharmacol.* Vol. 49, 725-734 (2009)

- «Absence of Effect of Telbivudine on Cardiac Repolarization: results of a Thorough QT/QTc Study in Healthy Participants» F. Poordad, …. & X.-J. Zhou, *J. Clin. Pharmacol.* Vol. 49, 1436-1446 (2009)

- «Baseline characteristics and early on-treatment response predict the outcomes of 2 years of telbivudine treatment of chronic hepatitis B» S. Zeuzem, …. & N. V. Naoumov, *J. Hepatology*, Vol. 51 (1), 11-20 (2009)

- «Early Viral Kinetics of Telbivudine and Entecavir: Results of a 12-Week Randomized Exploratory Study with Patients with HBeAg-Positive Chronic Hepatitis B» D. J. Suh, …. & S. Zeuzem, *Antimicrobial Agents and Chemotherapy*, Vol. 54 (3), 1242-1247 (2010)

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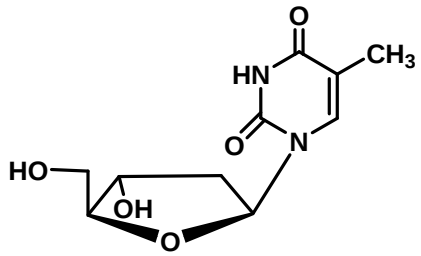
http://www.idenix.com

TELBIVUDINE (LdT) REGULATORY FILINGS

NOVARTIS
http://www.novartis.com

On December 2005 and February 2006, Idenix and Novartis submitted a New Drug Application (NDA) and a Marketing Authorization Application (MAA), respectively to the US Food and Drug Administration (FDA) and the European Medicine Agency (EMEA) seeking marketing approval for a 600 mg dose of



TELBIVUDINE (LdT)

as an oral, once-daily drug for the treatment of chronic hepatitis B.

Idenix LABORATOIRES
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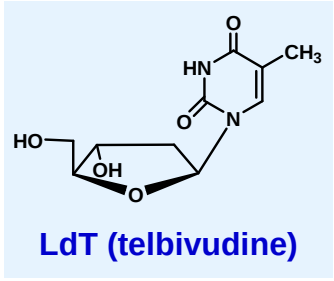
TELBIVUDINE (LdT) APPROVALS (1)

NOVARTIS
http://www.novartis.com



LdT (telbivudine)

On October 25, 2006, TELBIVUDINE (LdT) received FDA approval to be launched and sold in US under the brand name of

Tyzeka telbivudine 600 mg tablets

as a new once-a-day oral treatment for patients with chronic hepatitis B

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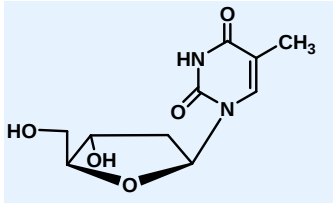
TELBIVUDINE (LdT) APPROVALS (2)

NOVARTIS
http://www.novartis.com

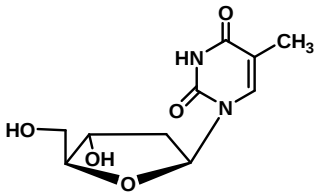


LdT (telbivudine)

On April 24, 2007, TELBIVUDINE (LdT) received European Commission approval to be launched and sold in all the 27 countries of the European Union (as well as Iceland and Norway) under the brand name of

Sebivo telbivudine

as a new once-a-day oral treatment for patients with chronic hepatitis B



LdT (telbivudine)

TELBIVUDINE (LdT) CURRENT STATUS

NOVARTIS
http://www.novartis.com

Effective October 1, 2007, Novartis Pharma AG assumed full responsibilities for the development, manufacturing and commercialization activities for

TYZEKA® (US)

and

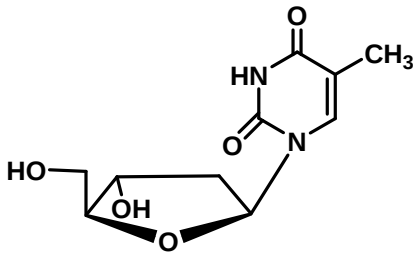
SEBIVO® (rest of world)

Currently, TELBIVUDINE (LdT) is also approved as SEBIVO® in more than 90 other countries, including Canada, Switzerland and China

TELBIVUDINE, A POTENT AND SPECIFIC ANTI-HBV NUCLEOSIDE ANALOGUE: FROM the BENCH to its MARKETING APPROVALS (TYZEKA®, SEBIVO®)

CONCLUSION

Tyzeka telbivudine 600 mg tablets



Sebivo telbivudine
Early Response. Predictable Performance.

LdT (telbivudine)

is an example of a fruitful collaboration between an academic team (Laboratoire de Chimie Organique Biomoléculaire de Synthèse, UMR 5625 CNRS – UMII) and a Company (Idenix, formerly Novirio)

For recent reviews on LdT (telbivudine), see:

- S. J. Hadziyannis, D. Vassilopoulos, *Expert Review of Gastroenterology and Hepatology,* Vol. **2** (1), 13-22 (2008)
- S. G. Lim, *Expert Review of Clinical Pharmacology*, Vol. **1** (2), 217-229 (2008)
- E. Palumbo, *Current Medicinal Chemistry – Anti-Infective Agents*, Vol. **7** (4), 245-248 (2008)
- Y. Y. N. Lui, H. L. Y. Chan, *Expert Opinion on Drug Metabolism & Toxicology*, Vol. **4** (10), 1351-1361 (2008)
- S. M. Tsunoda, T. Hassanein, *Future Virology*, Vol. **3** (6), 517-527 (2008)
- M. K. Osborn, *Therapeutic and Clinical Risk Management,* Vol. **5**, 789-798 (2009)
- P. Charuworn, E. B. Emmet, *Expert Clinical Medecine: Therapeutics,* Vol. **1**, 157-166 (2009)
- Y. Y. N. Lui, H. L. Y. Chan, *Expert Review of Anti-Infective Therapy*, Vol. **7** (3), 259-268 (2009)
- K. Nash, *Advances in Therapy*, Vol. **26** (2), 155-169 (2009)

TELBIVUDINE, A POTENT AND SPECIFIC ANTI-HBV NUCLEOSIDE ANALOGUE: FROM the BENCH to its MARKETING APPROVALS (TYZEKA®, SEBIVO®)

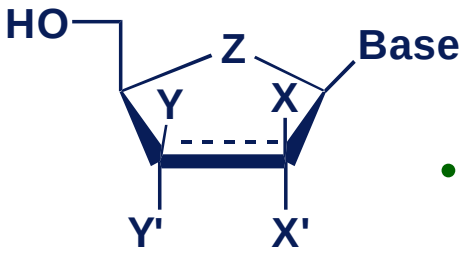
ADDENDUM

The significant results already obtained with nucleoside analogues in antiviral chemotherapy

AND

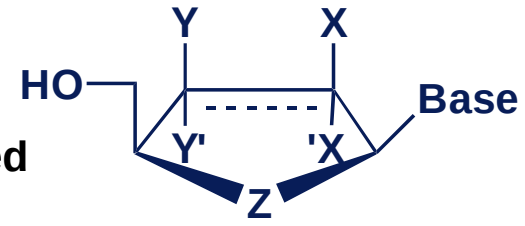
The seriousness of various viral infections (*not only HIV and HBV but also HCV and other emergent viruses*)

SYNTHESIS AND COMPARATIVE EVALUATION OF NEW β-D- and β-L-NUCLEOSIDE (and PRONUCLEOTIDE) DERIVATIVES



with

- **natural or modified purine and pyrimidine or other heterocycles**
- **natural, unnatural, modified, unsaturated and/or substituted sugar moiety**



Z = O, S, Se, …..; X, X ', Y, Y ' = OH, H, F, N_3, NH_2, double bond, …

A DREAM ?

ON THE WAY TO THE DISCOVERY OF NOVEL GENERATIONS OF ANTIVIRAL NUCLEOSIDE (and PRONUCLEOTIDE) DERIVATIVES

(endowed with potent and specific activity, lack of concomitant toxicity, and appropriate pharmacokinetic parameters, including high oral bioavailability)

« There's nothing wrong with fishing in science, providing you fish in fishy waters »

G. Gosselin (*adapted from a friend, Prof. Roger Guedj*)

TELBIVUDINE, A POTENT AND SPECIFIC ANTI-HBV NUCLEOSIDE ANALOGUE: FROM the BENCH to its MARKETING APPROVALS (TYZEKA®, SEBIVO®)

ACKNOWLEDGEMENTS

Concepts and Chemical Syntheses of L-nucleoside analogues:

FIRST: **Laboratoire de Chimie Organique Biomoléculaire de Synthèse**
1990-1998 [*Jean-Louis Imbach – Gilles Gosselin*]
Christophe Mathé (*Ph. D.*) **Claire Pierra (*Ph. D.* Student)**

THEN: **Laboratoire Coopératif Idenix - CNRS – Université Montpellier II**
1999-2006 [*Gilles Gosselin – Marie-Christine Bergogne*]
D. Dukhan (*Ph. D.*), C. Pierra (*Ph. D.*), S. Prad-Benzaria, and their tremendous teams

Pharmacology, Pharmacokinetics and Clinical Phase Studies:

Idenix Pharmaceuticals, Cambridge (USA)

N. Brown, *M.D.** **M. Bryant✞ *M.D., Ph. D.*** **E. Cretton-Scott, *Ph. D.****
A. Juodawlkis* **L. Placidi, *Ph. D.**** **M. Seifer, *Ph. D.***
J.-P. Sommadossi, *Ph. D.* **D. Standring, *Ph. D.*** **X.-J. Zhou, *Ph. D.***

*Former employee of Idenix Pharmaceuticals, Inc. ✞ *Deceased on March 04, 2002*

And Many Other World-wide Collaborations

International Society for Nucleosides, Nucleotides and Nucleic Acids (IS3NA)

FOUNDERS : P. D. Cook, G. Gosselin, P. Herdewijn, A. Matsuda, J. A. Secrist

* **MADE OFFICIAL on January 1st, 2001, Currently more than 350 registered members**

* **AIMS : Focused on research related to nucleic acid components and analogues, to encourage international collaborations on research and application among academic, industrial, governemental and private institutional organizations.**

PRELIMINARY IS3NA MEMBERSHIP BENEFITS :

- **Sponsoring the XIX International RoundTable (IRT) to be held in Lyon on 29th Aug - 3rd Sept, 2010**
- **Offering *Nucleosides, Nucleotides & Nucleic Acids* and other *Journals* at reduced rates**

VISIT ITS WEBSITE and JOIN THE IS3NA
http://www. is3na.org

- Board - Committees	By-Laws	- Job advertisements - Highlights	Membership Application Form

Tyzeka®/Sebivo® (telbivudine)
Indication and Safety Information

- Telbivudine is indicated for the treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease.
- Risk of severe acute exacerbation of hepatitis B post treatment; hepatic function must be monitored for at least several months after treatment discontinuation
- Risks of lactic acidosis and hepatomegaly with steatosis
- Risk of myopathy: discontinue treatment if myopathy is diagnosed; caution with co-administration of agents associated with myopathy
- Uncommon risk of peripheral neuropathy (PN): if suspected reconsider treatment
  - Increased risk of PN when co-administered with PegIFN alfa-2a or other IFNs
- Caution in patients with impaired renal function, and when used with drugs that affect renal function
- Limited data available in elderly and individuals with HIV coinfection
- Use in children under 16 years and individuals with lamivudine resistance is not recommended
- Use during pregnancy only if the benefit to the mother outweighs the potential risk to the fetus. Do not breastfeed
- Rare occurrence of rhabdomyolysis in post-marketing setting

SEBIVO® (telbivudine) Summary of Product Characteristics. Novartis Pharma AG. September 2009.