Body Burden 2,3,7,8-TCDD and Human Common Viruses: Chemico-Biological Interactions Associated with Malignancies in Arctic Residents

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Human viruses associated with infections in the Arctic

(all infect cells and establish latent infections)

Hepatitis B virus

Epstein-Barr virus

Papillomavirus

Cytomegalovirus

Virus-associated cancers in the Arctic

✓ **According to the US CDC, the rate of hepatitis B lesions has been high among Alaska Natives, and the annual incidence of hepatocellular carcinoma (HCC) among Eskimo males was five times that of white males in the United States.** [McMahon et al., *Hepatology* 2000]. **Among 1,400 Alaska Native the Hepatitis B virus (HBV) carriers, the relative risk factor of developing HCC was 148 compared to the general population** [McMahon et al. *Ann Intern Med* 2001]

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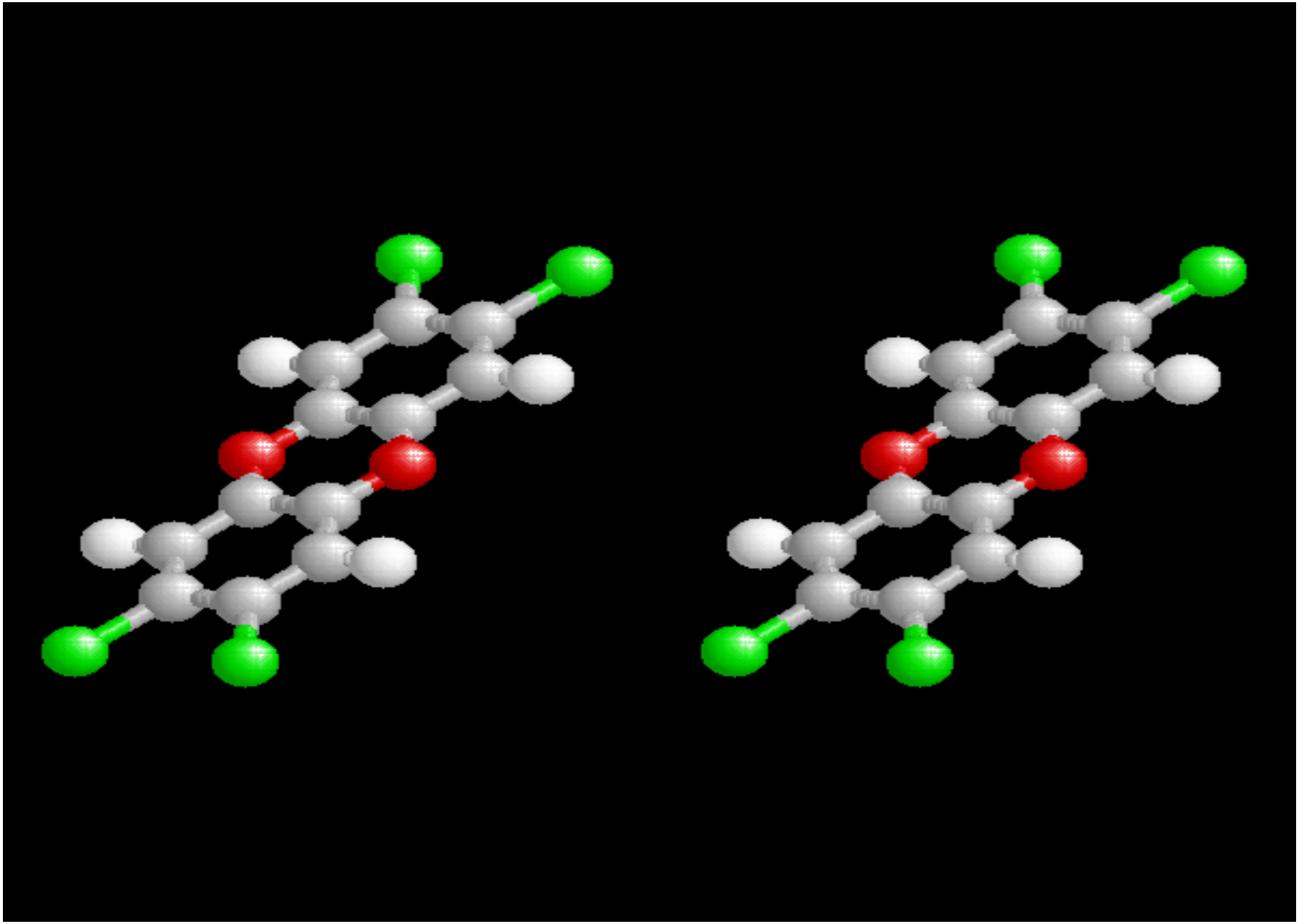
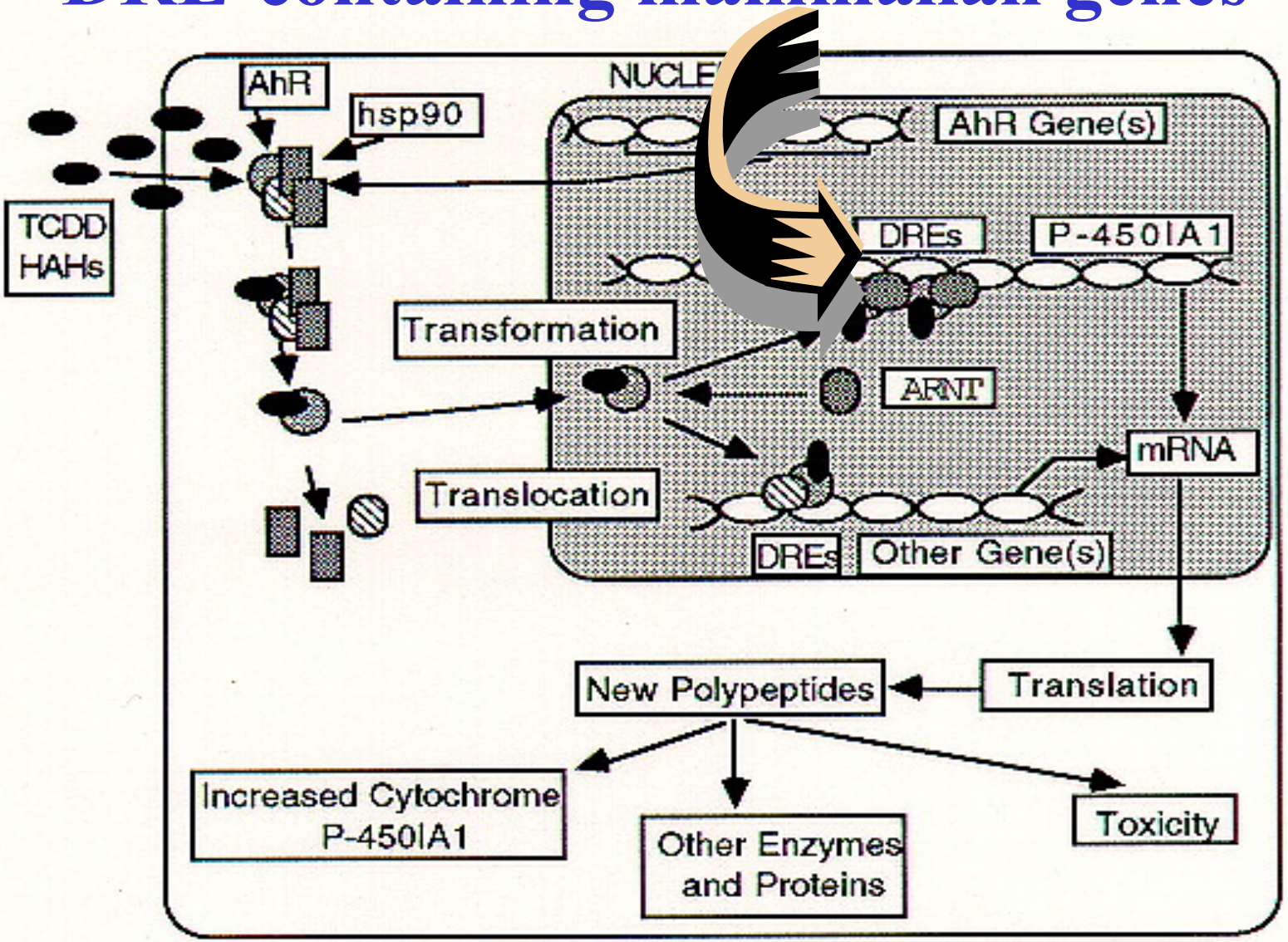
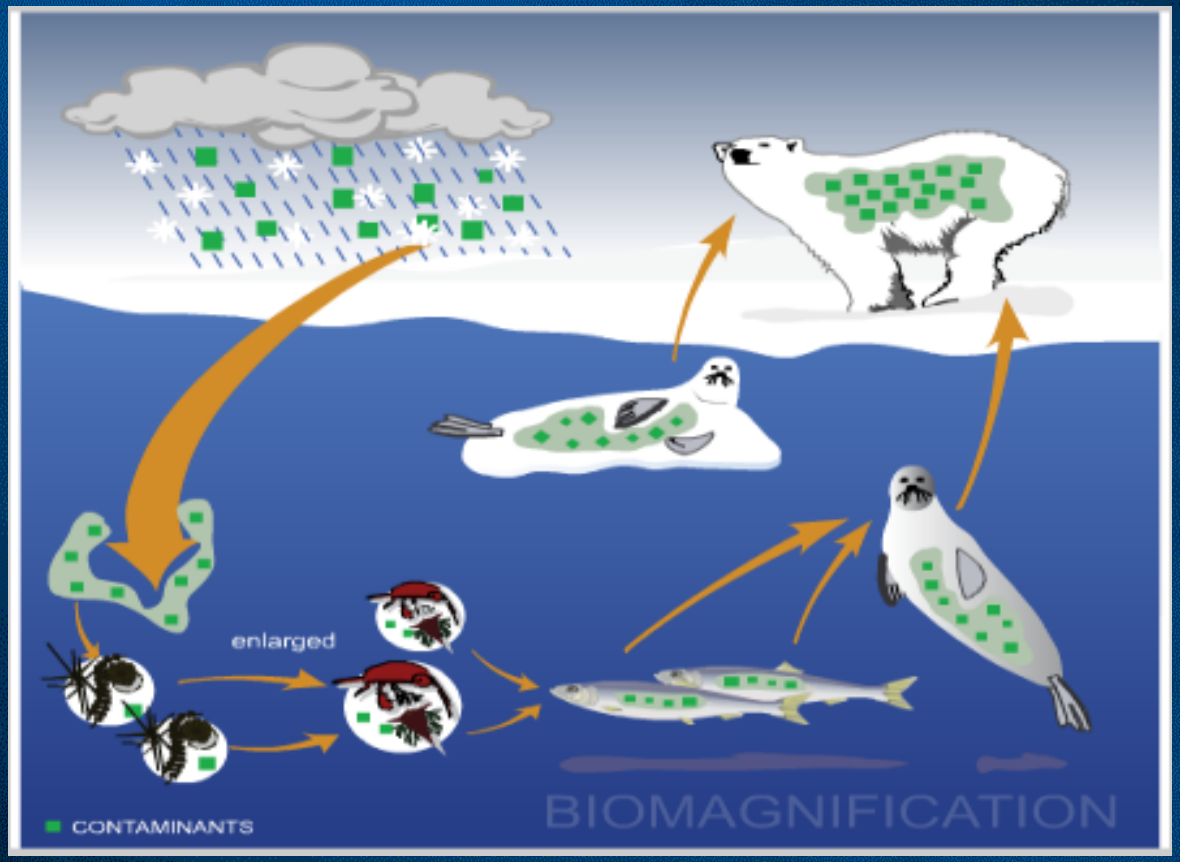


Molecular mechanism of TCDD action on DRE-containing mammalian genes



Airborne Long Range Transport

Highest risks for top predators



Dioxins are soluble in lipids. Marine food chain: rich in lipids

Dioxins in the Arctic diet

✓ **The importance of diet on exposure and health effects of dioxin-like compounds in the Arctic has been recently reviewed** [Odland et al., *Acta Paediatr* 2003]

✓ **The mean total body burden (concentration of dioxin-like compounds expressed in 2,3,7,8-TCDD toxic equivalents) in Inuit people of Arctic Quebec is 7 times of that in people of South Quebec, whereas among fishermen it might reach 25 times of controls. However, "although the body burden of dioxin-like compounds are close to those induced adverse effects in laboratory animals, dietary benefits from sea-food based diet outweigh the hypothetical health risks"** [Dewailly et al., *Envir Health Perspect* 1994; Ayotte et al., *Chemosphere* 1997]

- **2,3,7,8-Tetrachlorodibenzo-p-dioxin as a possible activator of HIV infection**
  A.G. Pokrovsky, A.I Chernykh, O.N. Yastrebova, and I.B. Tsyrlov
  Biochem. Biophys. Res. Commun. 179:46-51, 1991

- **Stimulatory effect of the CYP1A1 inducer 2,3,7,8-tetrachlorodibenzo-p-dioxin on the reproduction of HIV-1 in human lymphoid cell culture**
  I.B. Tsyrlov and A.G. Pokrovsky. *Xenobiotica* 23:457-467, 1993

- **Activating effects of dioxin on HIV-1 in human CD4+ lymphoid cells**
  I.B. Tsyrlov and A.G. Pokrovsky. *Proceed. 10th Intern. Conf. AIDS* (Yokohama, Japan) 10:127, 1994

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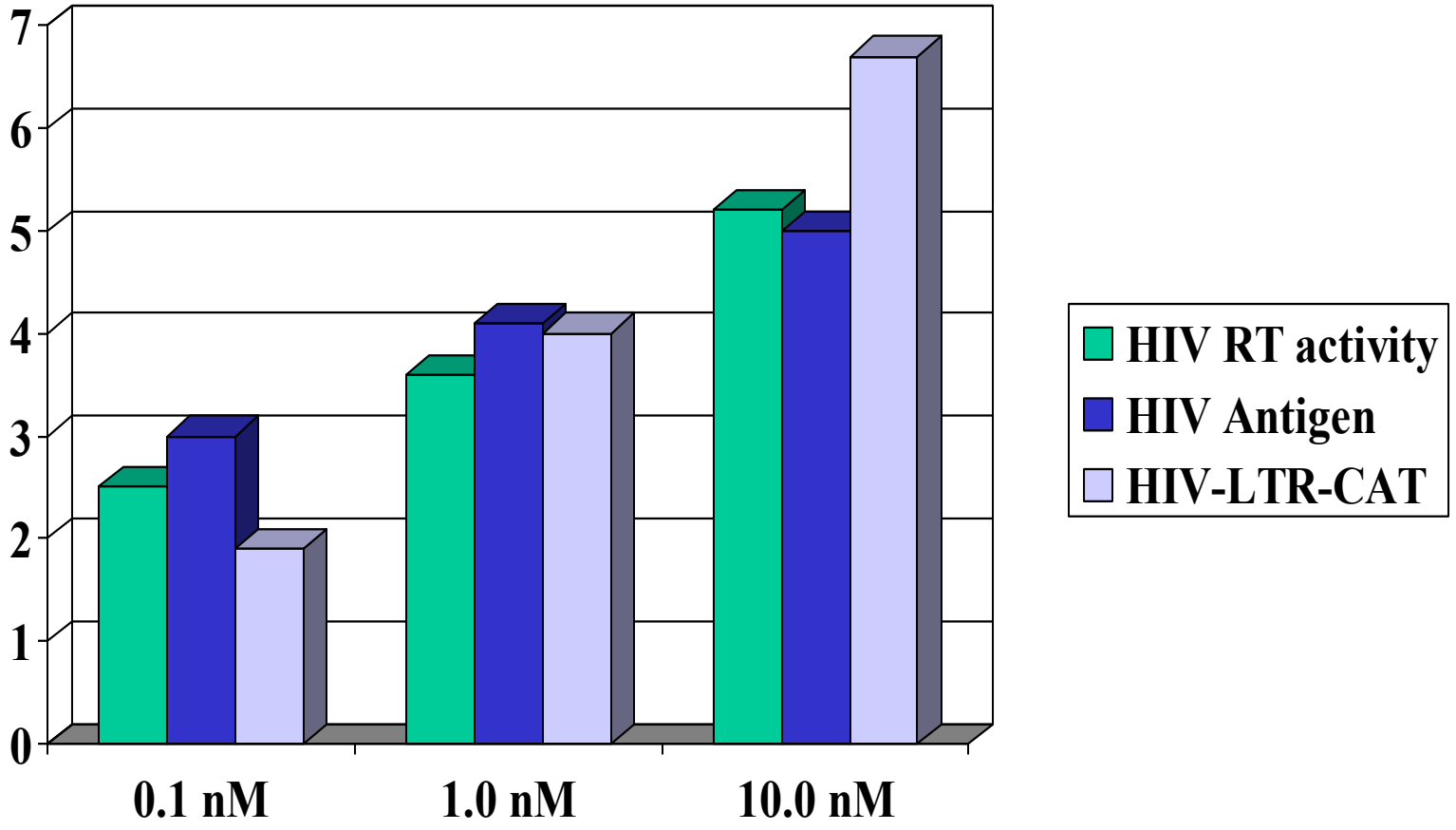

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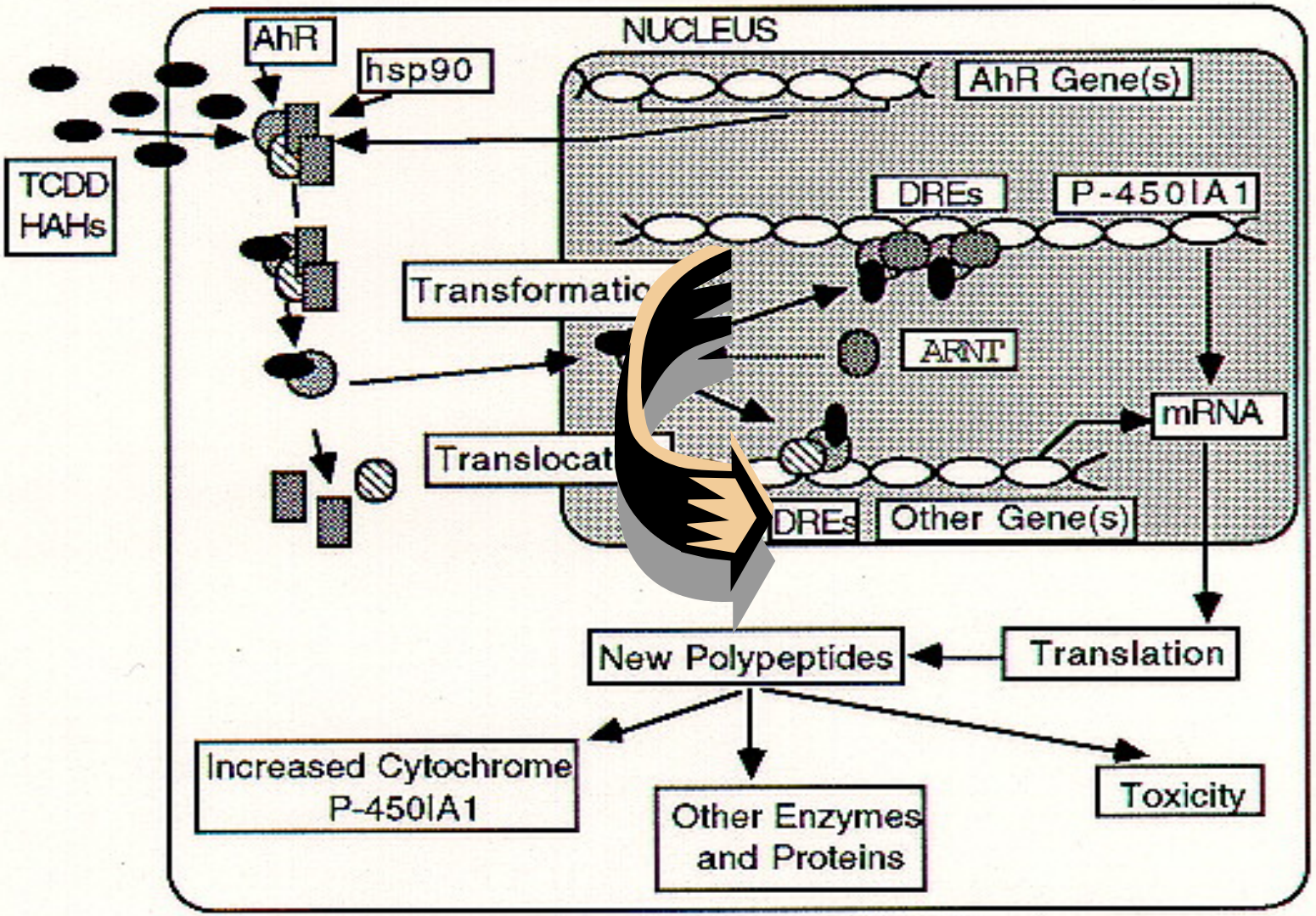
Molecular mechanism of TCDD action on viral DRE-containing genes ("Other Genes")



A picomolar TCDD activates replication of human cytomegalovirus (CMV)

(From: Murayama et al., *BBRC* 296:651-656, 2002)

- **About 4-fold enhancing effect on CMV production was observed in MRC-5 cells treated with 0.0001 pg TCDD/ml (0.3 pM TCDD)**

- **Enhancement of the CMV DNA replication was determined with at least 0.01 pg TCDD/ml (30.0 pM TCDD)**

- **CMV-infected cells expressed transcripts of the AhR and AhR nuclear translocator. The anti-AhR antibody reduced TCDD-enhanced CMV replication to un-stimulated levels**

Cancer-associated human viruses having multiple promoter DREs

(viruses related to malignancies in the Arctic are marked with ¶)

Virus name	Promoter DREs (#)	TCDD/**(AhR overexpressed)	Virally derived cancers
¶Cytomegalovirus	10	0.3 pM/**	Colon adenocarcinoma Colorectal polyps Congenital cancer Breast cancer in women < 40 yr
¶Epstein-Barr virus	22	?/**	Non-Hodgkin's Lymphomas, Sarcomas Nasopharengeal sarcoma Burkett's lymphoma
Herpes simplex virus			
type 1	30	?/?	
type 2	8	?/?	Cervical Cancer?
¶Hepatitis B virus	4	?/**	Hepatocellular carcinoma

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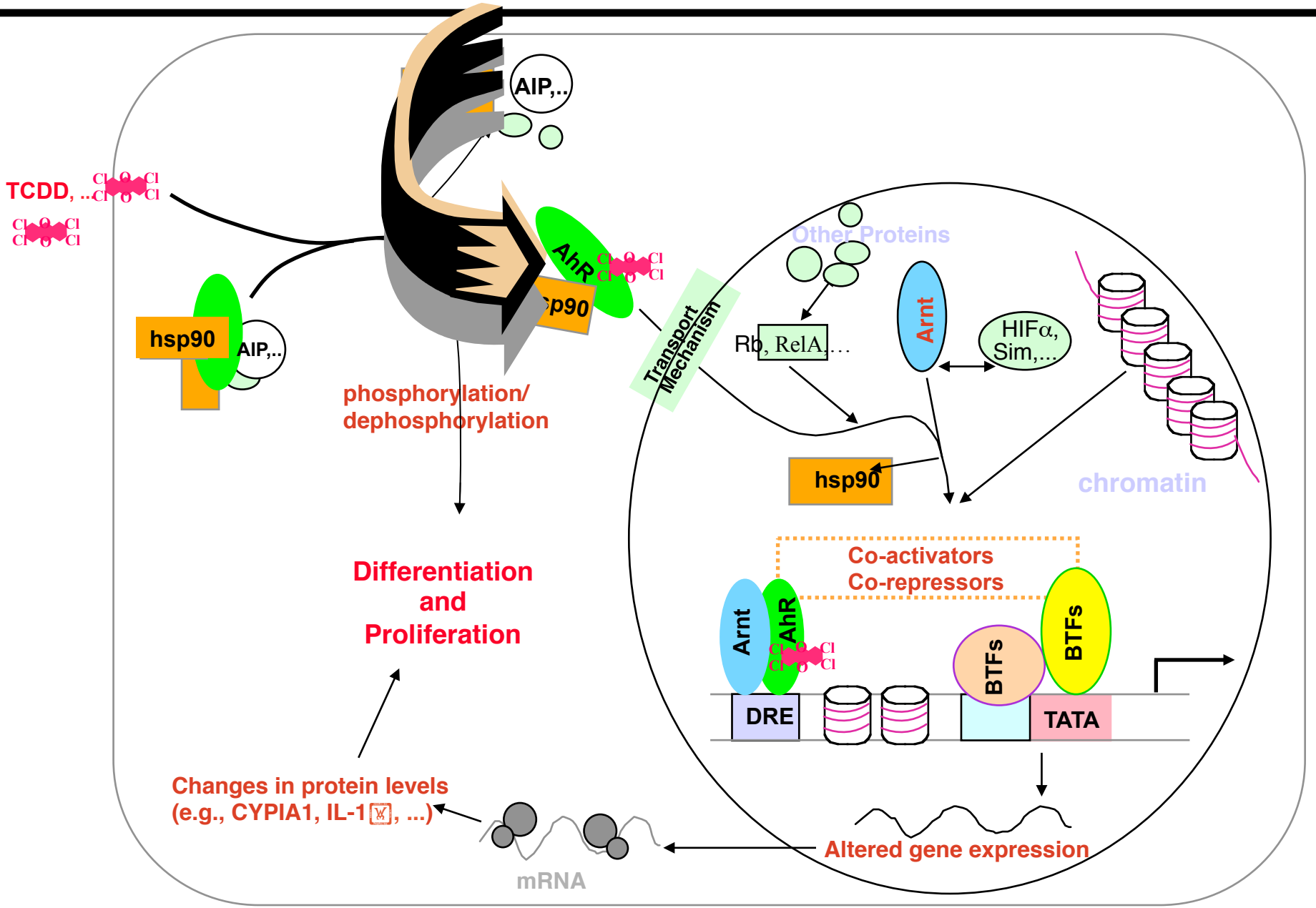
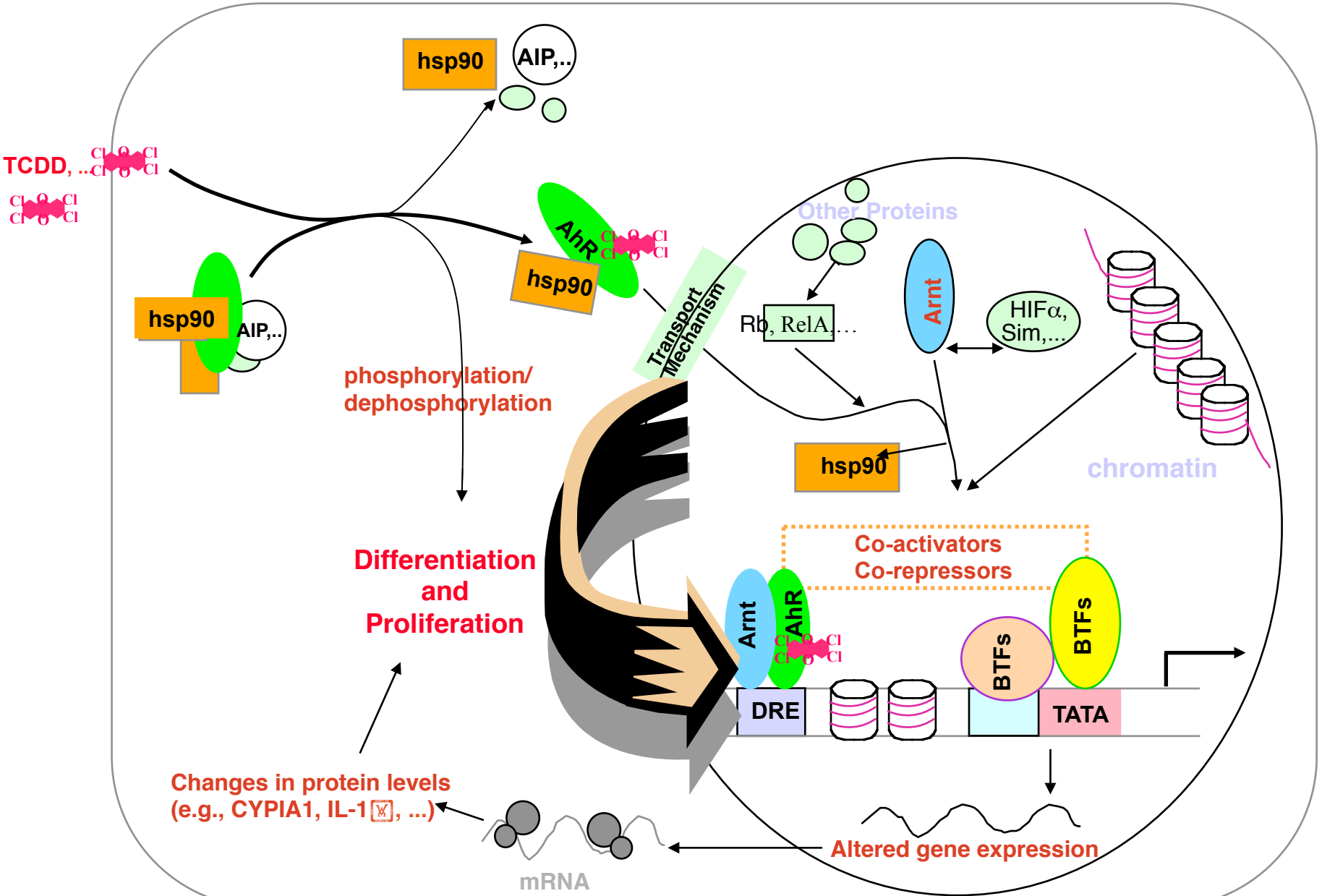
HIV type-1	1	**0.1-1.0 nM/****	Various malignancies in the context of HIV-1 infection
¶Papillomavirus type 16	1	/**	Invasive cervical cancer Skin cancer Oral & laryngeal cancers Anal cancer
T-lymphotropic virus type 1	1	/**	Adult T-cell leukemia (ATL)

The AhR as a treatment target of virus-associated human cancers with bioflavonoids or indole-3-carbinol

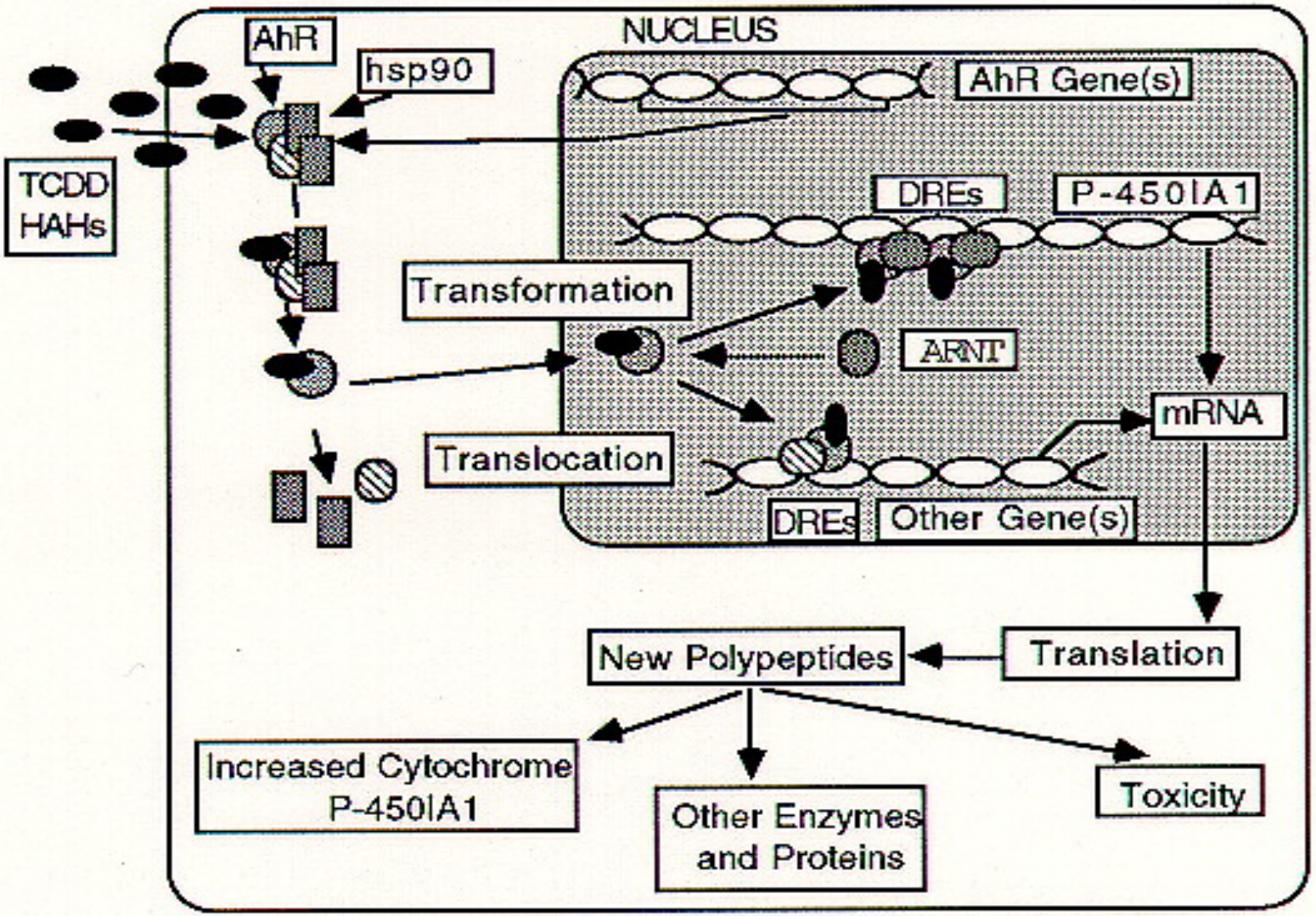


Viral DRE as a potential target for the treatment of virus-associated human malignancies with salycilamide




NO
FISHING
POISON

Molecular mechanism of TCDD action



Molecular and Cellular Biology 24:1799–1808, 2004

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Gilad Doitsh and Yosef Shaul*

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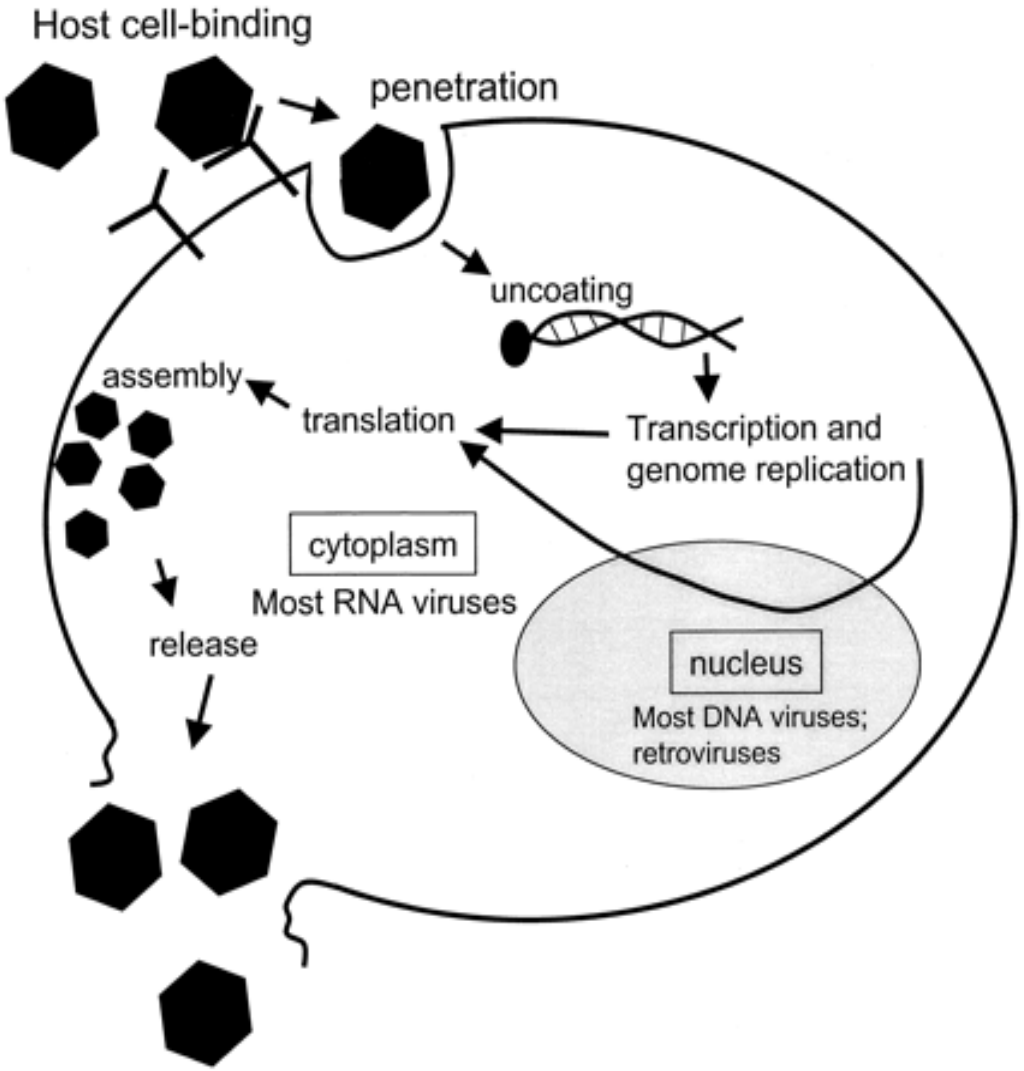
The data provides strong evidence for the role of EnhI in regulating global and temporal HBV gene expression.

General model of eukaryotic viral replication



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Dioxin-like compounds in the Arctic

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✓ **A high level of these compounds are reported among Arctic top predators** [Pusch et al., *J Environ Monit* 2005]

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Human viral infections in the Arctic

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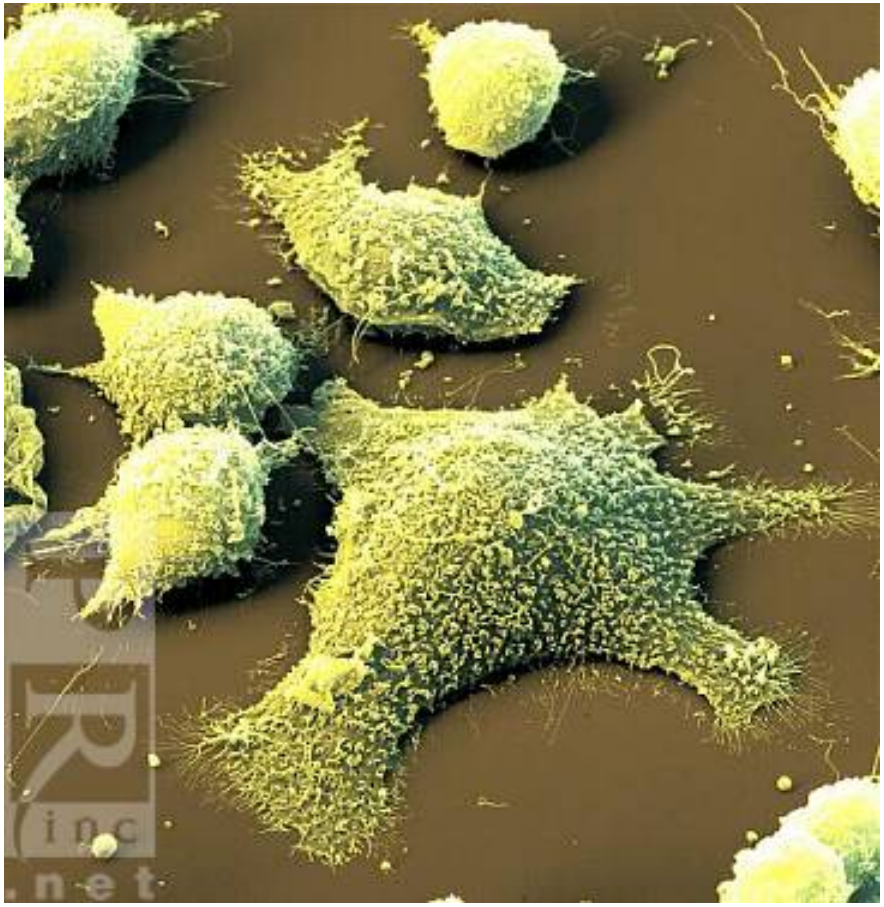
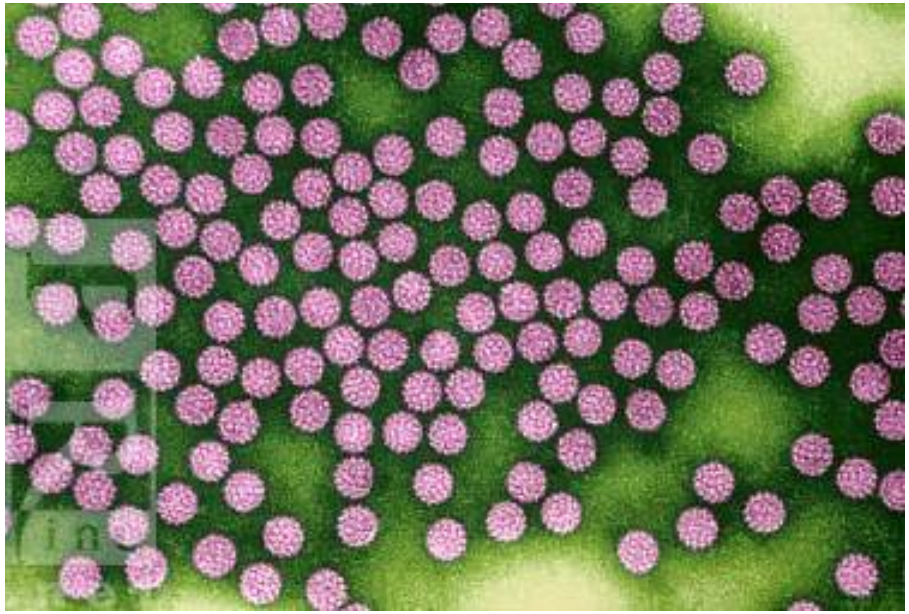
Papillomavirus

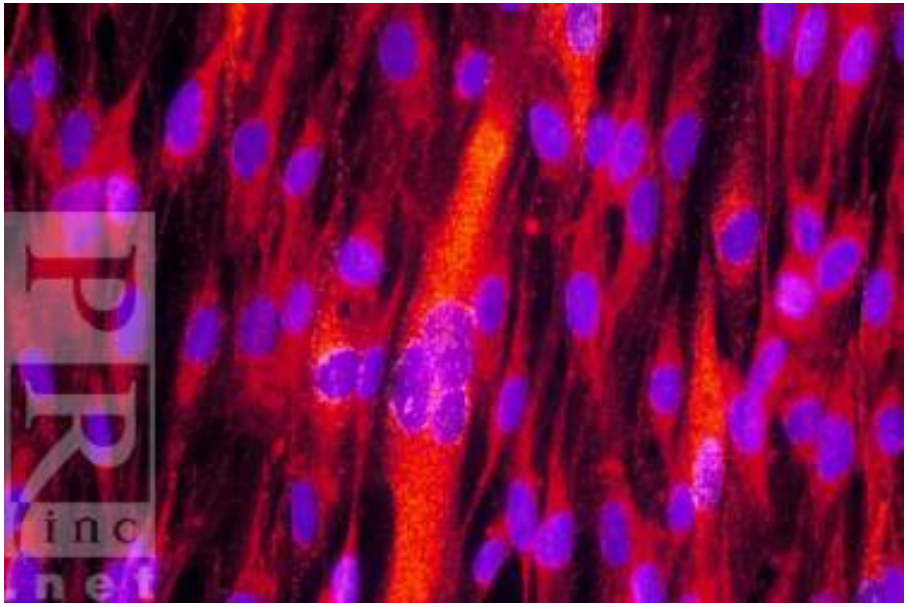
Cytomegalovirus



Color-enhanced transmission electron microscopy (magnification 27,000x) of negatively stained human papillomavirus, isolated from common warts.

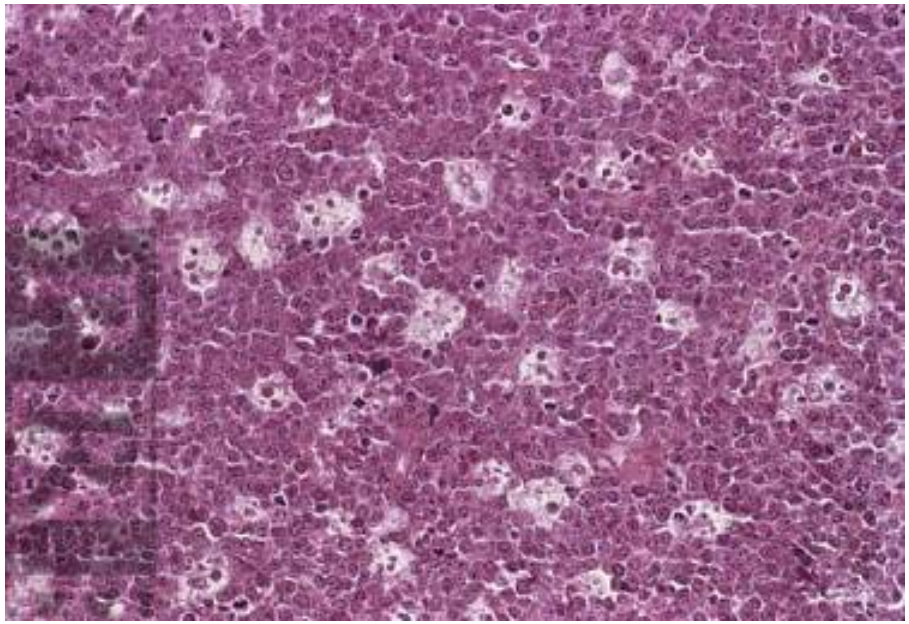


Cytomegalovirus infected cells



Immunofluorescent light micrograph of human cells infected with cytomegaloviruses. The infected cells are shown by the presence of the virus-specific protein UL37 (orange). Cell nuclei are blue, with mitochondria red.

Burkitt's lymphoma cancer

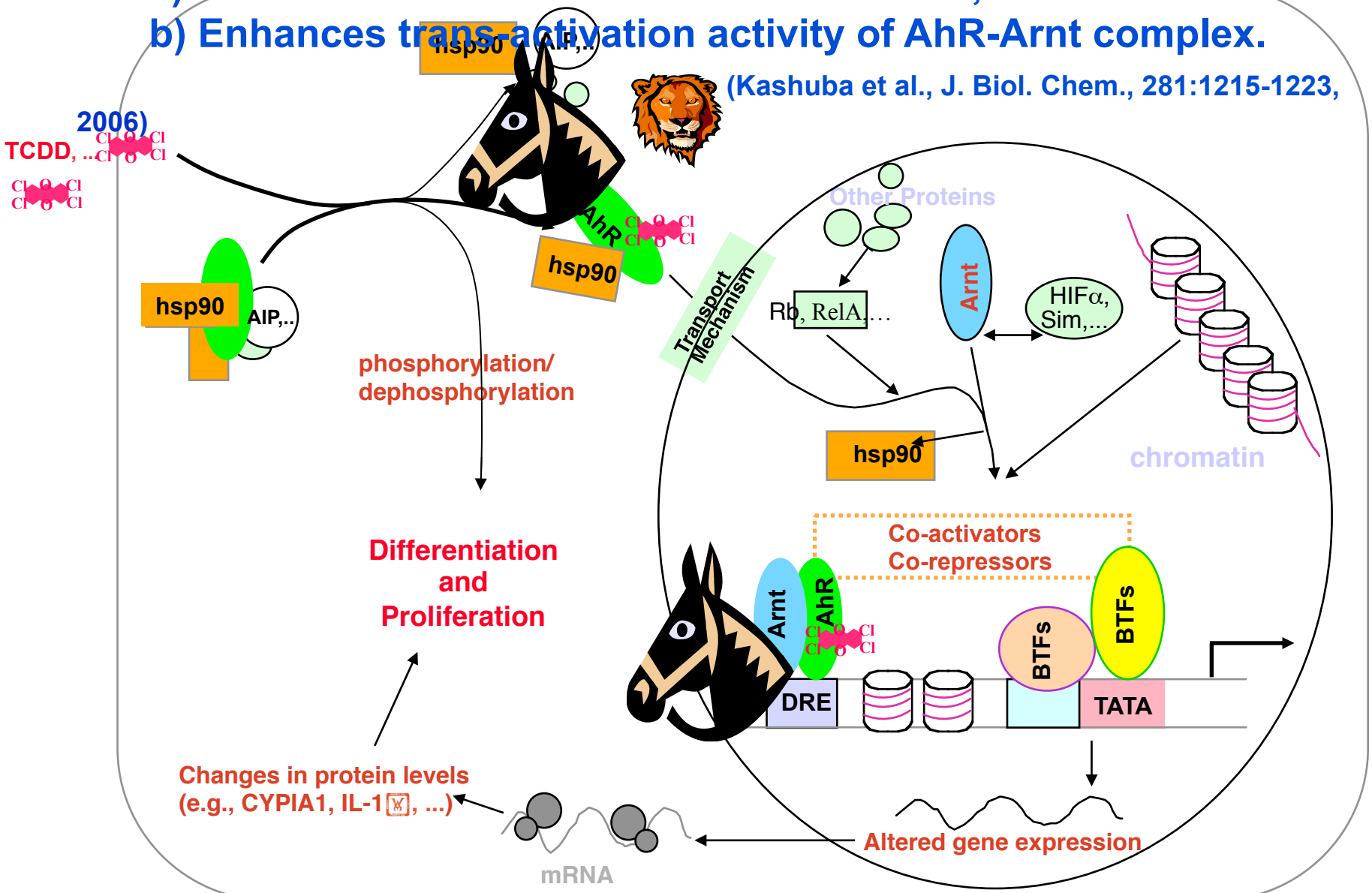


Numerous large, pale macrophages are present, and the small cancerous cells have numerous dark nucleoli within them. This cancer is caused by infection with the Epstein-Barr virus.

Effect of EBV-encoded EBNA-3 :

a) Counter-acts effects of XAP2 on the AhR;
b) Enhances trans-activation activity of AhR-Arnt complex.

(Kashuba et al., J. Biol. Chem., 281:1215-1223, 2006)



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Probability of Developing Invasive Cancers Within Selected Age Intervals (in %, US, 2000-2002)

		Birth to 39	40 to 59	60 to 69	70 and older	Birth to Death
All sites	Male Female	1.43 1.99	8.57 9.06	16.46 10.54	39.61 26.72	45.67 38.09
Colon & rectum	Male Female	0.07 0.06	0.90 0.70	1.66 1.16	4.94 4.61	5.84 5.51
Non-Hodgkin lymphoma	Male Female	0.14 0.09	0.47 0.31	0.56 0.42	1.57 1.29	2.18 1.82
Uterine cervix	Female	0.15	0.28	0.15	0.22	0.74

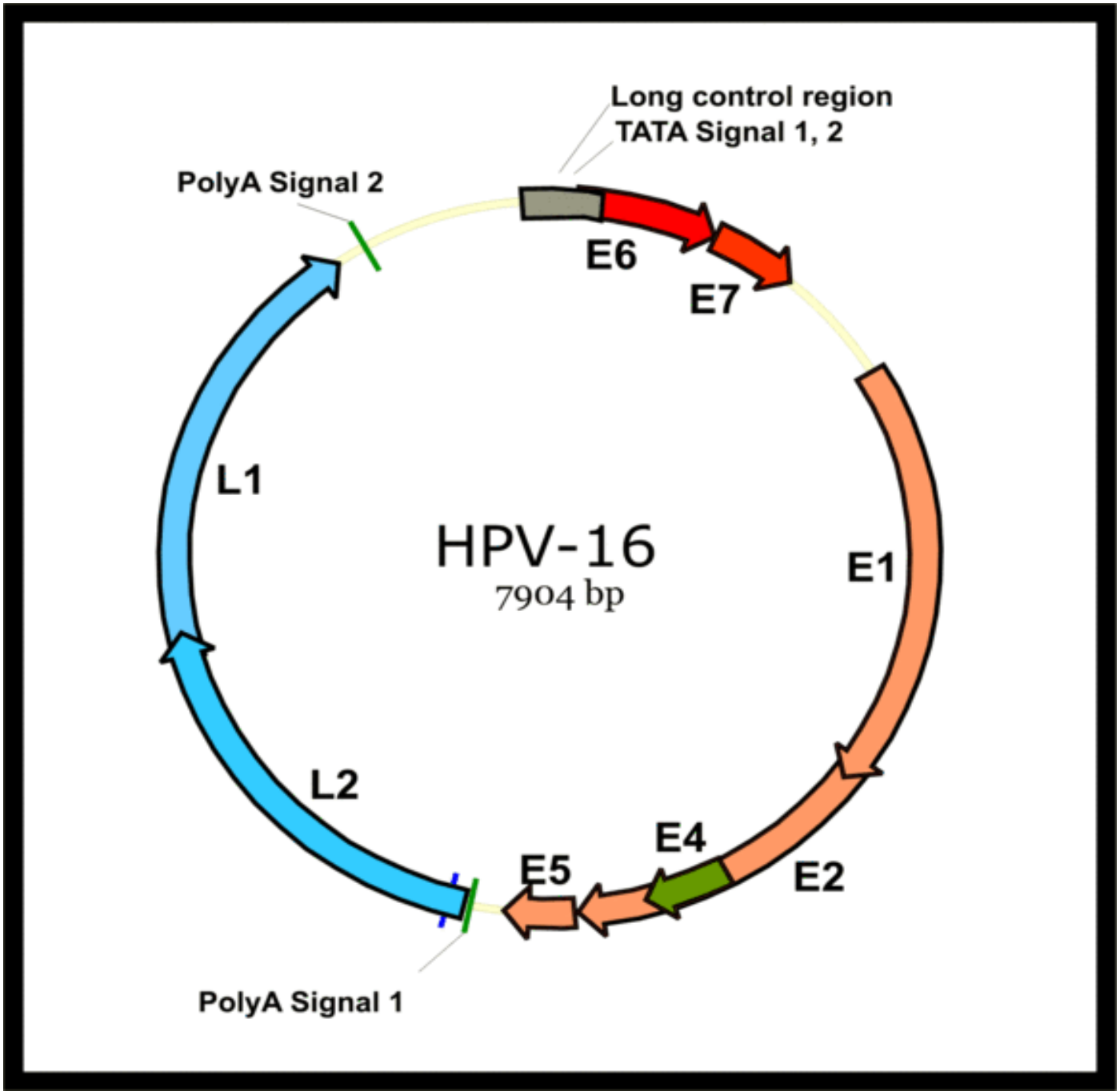
Nearly All Vertebrate Animals Examined Respond to Dioxins

What about People?

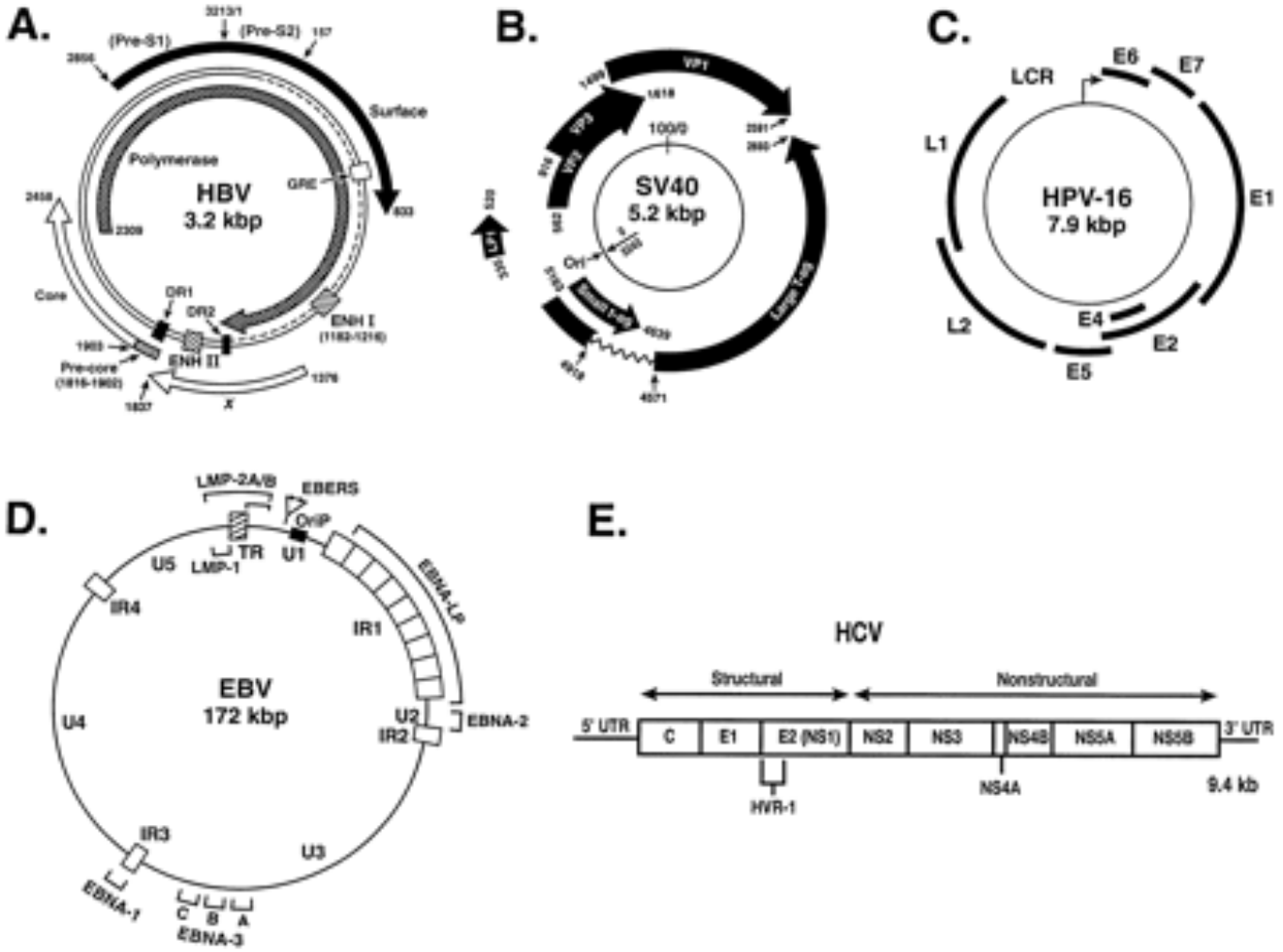
- **People have the Ah Receptor and the other members of its signaling complex.**
- **Subtle effects have been detected in the General Population.**
- **Adverse effects have been seen in highly exposed populations.**

THE REAL QUESTION IS NOT CAN PEOPLE RESPOND TO DIOXINS, BUT AT WHAT DOSES THEY RESPOND!

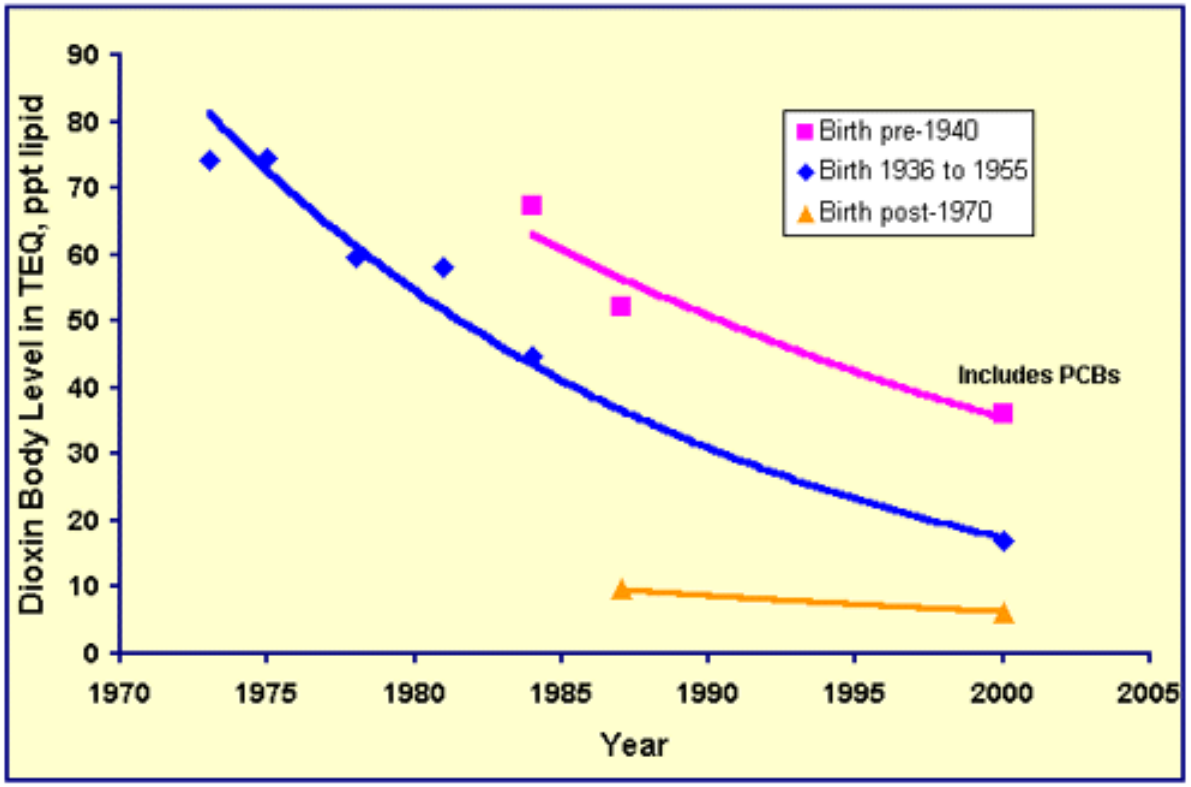
Genomic structure of human papillomavirus



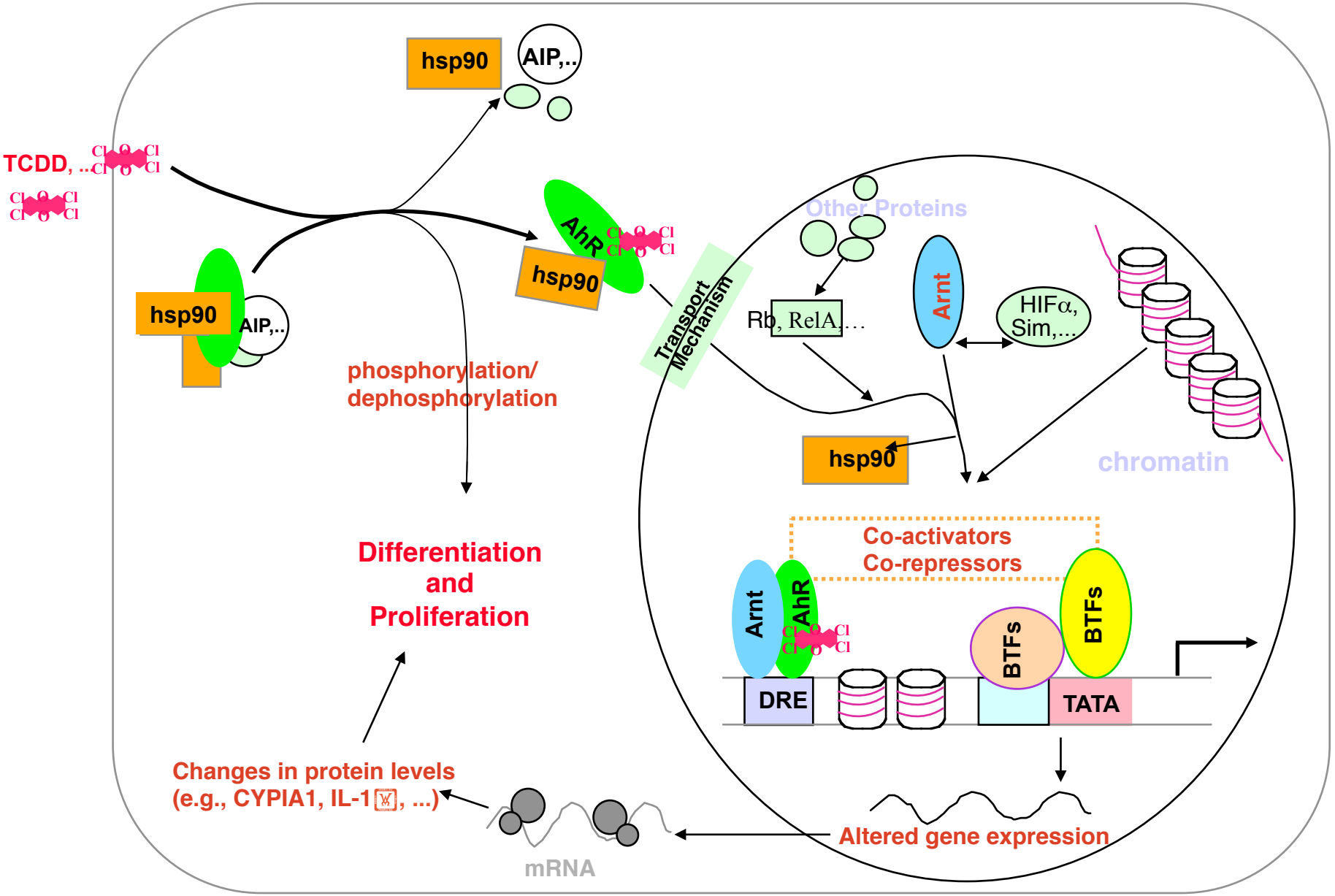
Genome maps of human tumor viruses



Trends in Body Levels of Dioxins



Mechanism of TCDD Action



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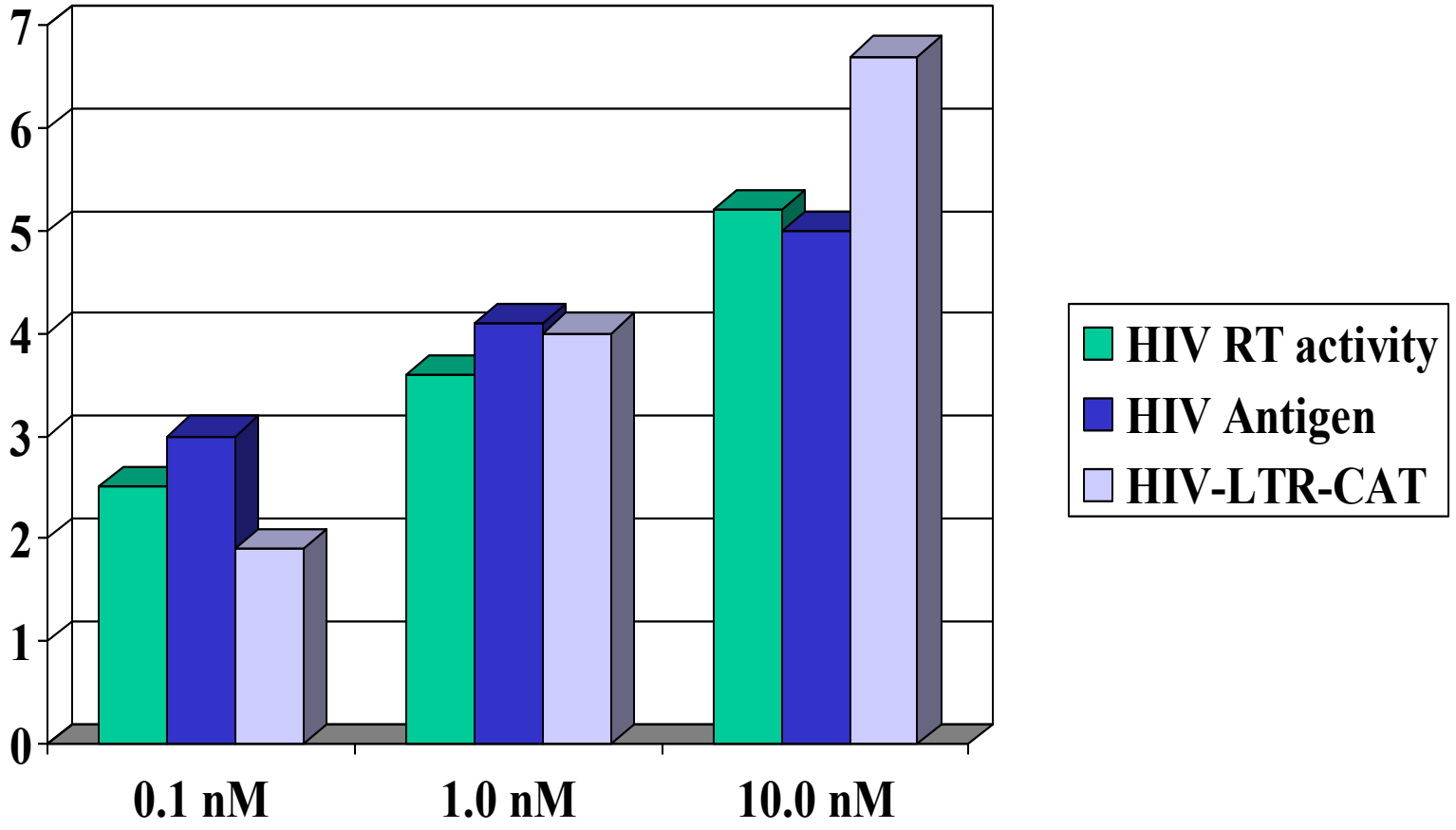
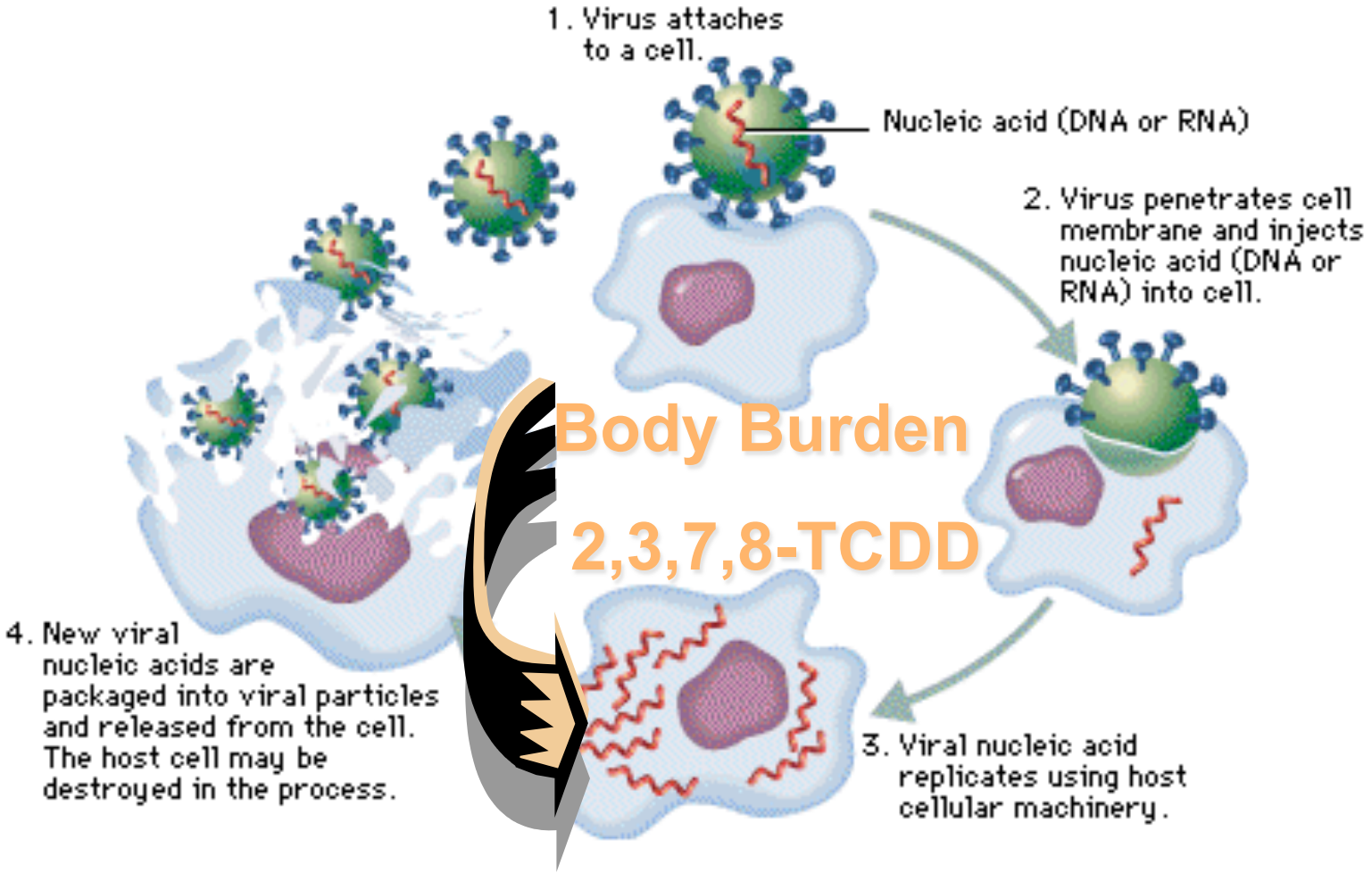


Viral Replication Cycle



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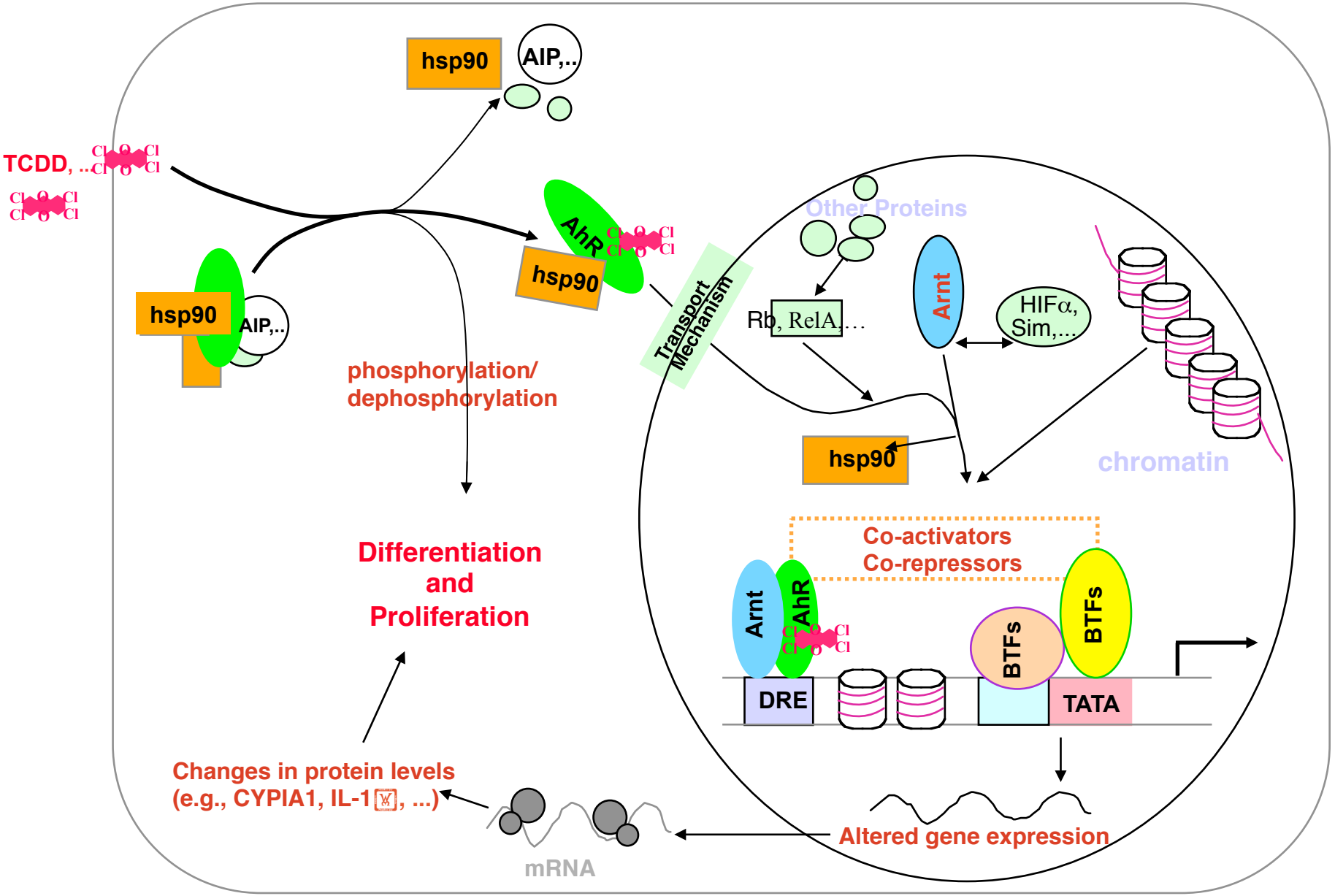

RESEARCH & DEVELOPMENT

Building a scientific foundation for sound environmental decisions