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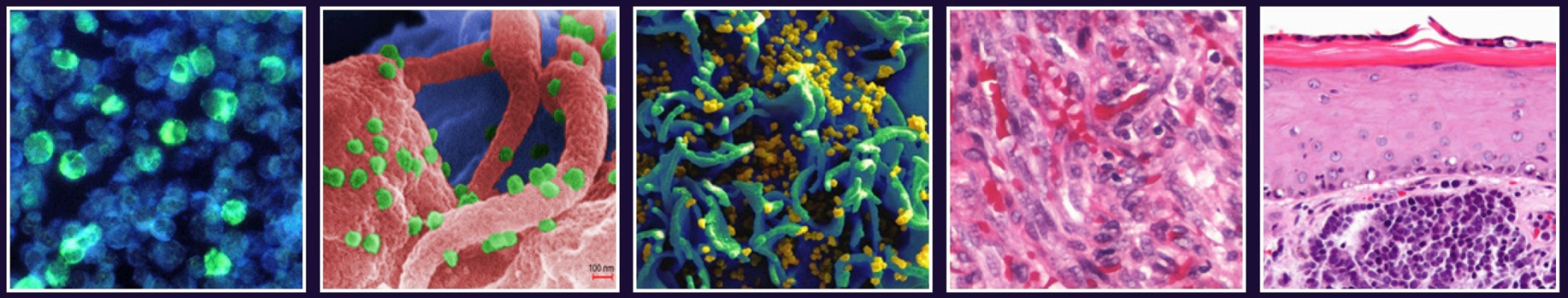

Selected Viruses Overarching Issues

Gloria D. Jahnke, DVM, DABT
Office of the RoC, NIEHS

NTP Peer Review Meeting
December 17, 2015

Virus Evaluations

- Issues
  - High prevalence of infection (EBV, MCV)
  - Cofactors may affect cancer outcome: e.g., immunosuppression, other infectious agents, host genetics
  - Cancer endpoint defined by the presence of virus (adult T-cell leukemia/lymphoma and HTLV-1 or primary effusion lymphoma and KSHV).

Factors to Consider

- Human epidemiology studies
  - Hill considerations
- Molecular information (clinical studies)
  - Monoclonality of virus in malignant tissue, e.g., (1) clonal immunoglobulin gene rearrangements (EBV), (2) size of the fused terminal repeat region is specific for each viral clone (KSHV and EBV), or (3) integration pattern of provirus into host chromosome DNA (HTLV and MCV).
    - Supports causality
    - Supports temporality
  - Evidence that the virus is expressing oncogenic protein.
  - Percentage of tumors positive for virus.

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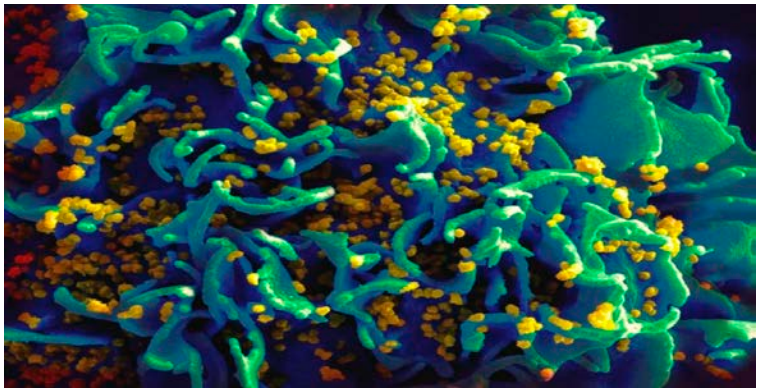
Draft RoC Monograph
Human T-Cell Lymphotropic Virus Type 1



Gloria D. Jahnke, DVM, DABT
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Human T-Cell Lymphotropic Virus Type 1

Outline

Properties and detection

Transmission and exposure

Mechanistic information

Human cancer studies

Preliminary level of evidence summary

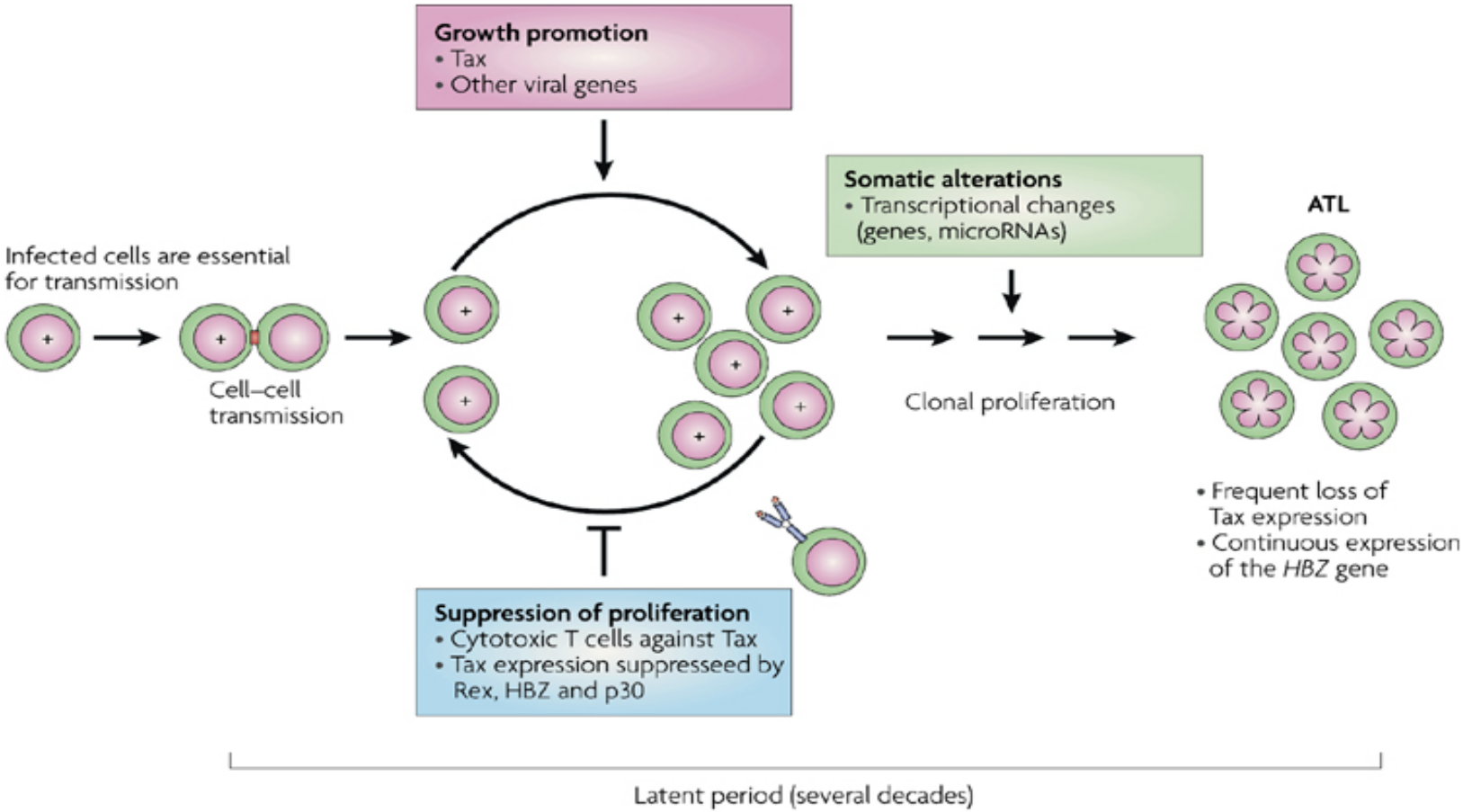
HTLV-1 Properties and Detection

- Retrovirus, single stranded RNA virus, enveloped
  - Four subtypes: HTLV-1, HTLV-2, HTLV-3, HTLV-4
  - HTLV-1 is only subtype associated with neoplasia
- Detection
  - Antibodies, DNA or RNA, in culture
  - Proviral load (amount of viral DNA/cell) correlates with disease onset

Significant U.S. Exposure

- HTLV-1 – U.S. blood donors (2000–2009) seroprevalence 0.0051% or approximately 16,000 people
  - Immigration can raise numbers in local populations in U.S.
  - In endemic areas – S.W. Japan, Caribbean Basin, Melanesia, parts of Africa, South America – prevalence can be 15%
  - Estimates of 15-20 million people infected worldwide
- Transmission
  - Transfer of infected body fluids such as semen and blood
  - Mother to child transmission – *in utero* and through breast milk
    - Breastfeeding has higher rate of transmission

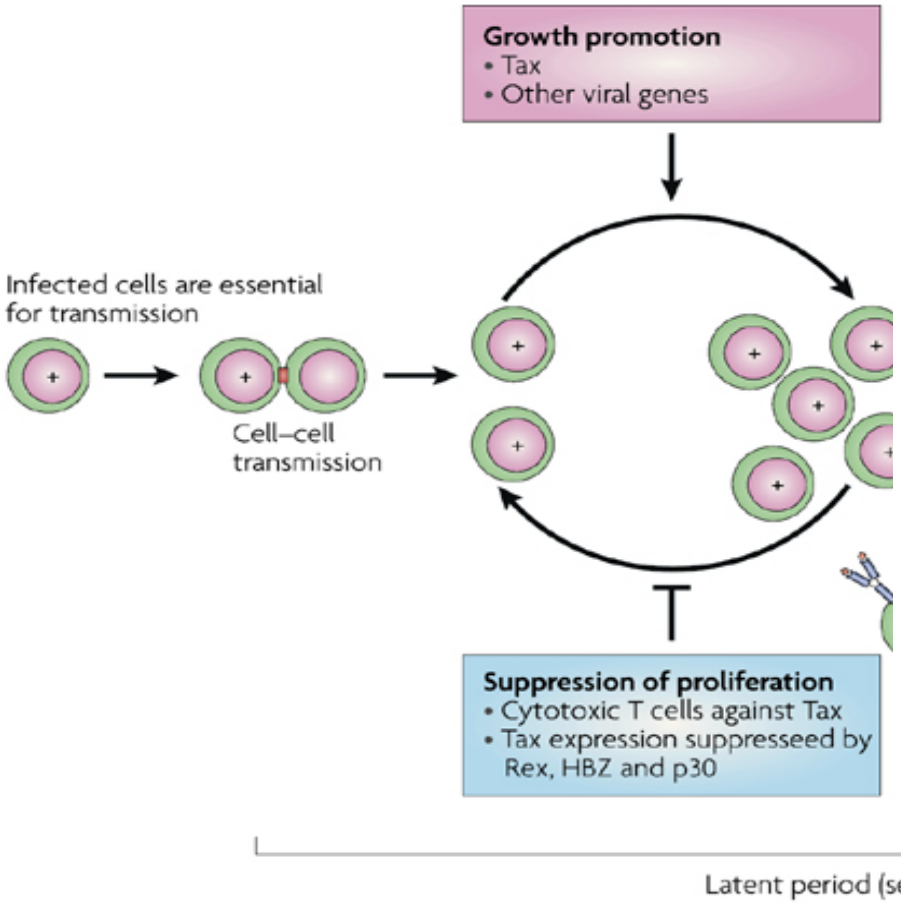
Pathogenesis of Adult T-cell Leukemia/Lymphoma



Infects mainly CD4 T cells; ~5% of HTLV-1 carriers develop adult T-cell leukemia/lymphoma

Nature Reviews | Cancer
Matsuoka and Jeang, April 2007

Pathogenesis of Adult T-cell Leukemia/Lymphoma



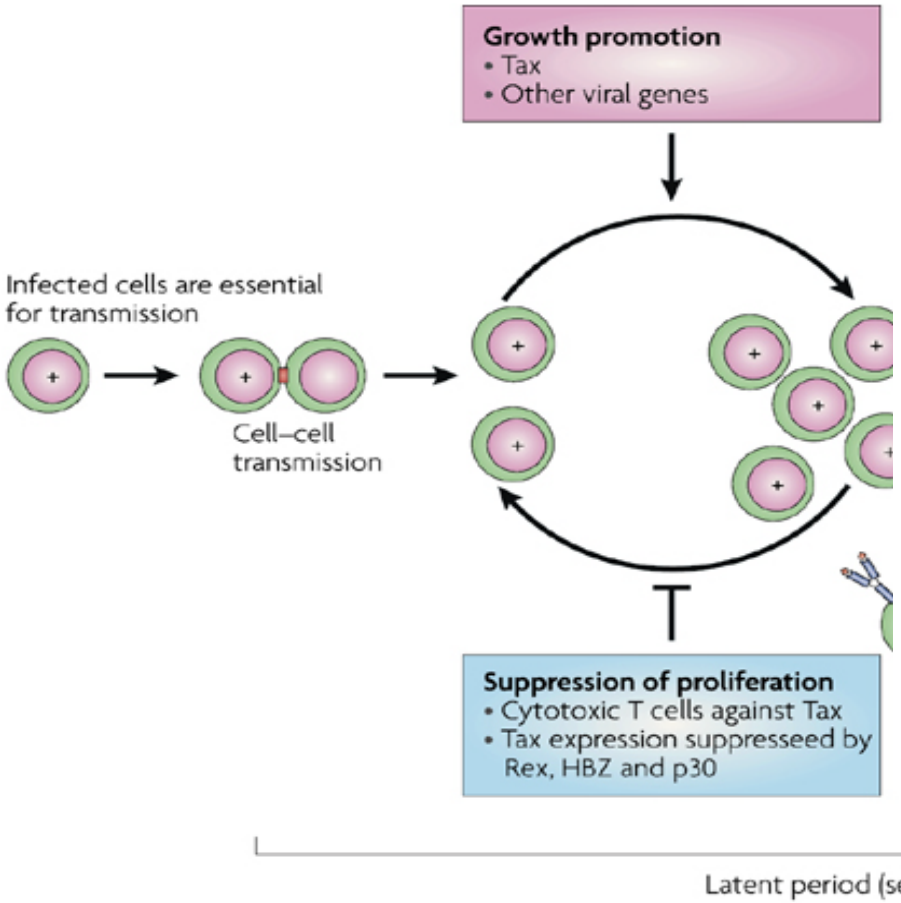
Tax

- Shown to immortalize human T cells both *in vitro* and *in vivo* in the absence of other viral factors
- Interacts with NF-kappaB proteins involved with T-cell proliferation, growth, survival
- Immunogenic

~5% of HTLV-1 carriers develop adult T-cell leukemia/lymphoma

Nature Reviews | Cancer
Matsuoka and Jeang, April 2007

Pathogenesis of Adult T-cell Leukemia/Lymphoma



HTLV-1 basic leucine zipper factor (HBZ)

- Maintains ATLL transformation
- Promotes immune evasion, cell survival, cell proliferation, and immortality
- Not immunogenic

~5% of HTLV-1 carriers develop adult T-cell leukemia/lymphoma (ATLL)

Nature Reviews | Cancer
Matsuoka and Jeang, April 2007

Assessment of Four Cancer Endpoints

- Adult T-cell leukemia/lymphoma
- Liver cancer
- Gastric cancer
- Cutaneous T-cell lymphoma
  - Inconsistent evidence, inadequate to assess.

Adult T-cell Leukemia/Lymphoma

Sufficient level of evidence from human studies

Epidemiology	
Positive associations	Originally link established by case reports/case series; over 550 cases primarily from Japan and South America (1985–2005)
	HTLV-1 carriers developed ATLL (8 cohorts)
	Risk higher with higher viral load or proviral load in 4 case-control studies nested in HTLV-1 cohort studies
Human tissue	
Clonality	Monoclonal
% HTLV-1 infected tumors	> 90%
HTLV-1 protein expression	40% Tax, 100% HBZ
Other	Diagnostic criteria for ATLL

Limited level of evidence from human studies

Epidemiology Positive associations	Positive associations in all studies (4 case-control and 2 cohort studies) Positive findings in studies that excluded or controlled for history of blood transfusion One study found HTLV-1 increased risk of HCV-associated cancer in men Exposure-response (increasing risk with increasing antibody level found in one study) Consistent evidence of increased risk but bias and confounding can not be ruled out.
Human tissue Clonality % HTLV-1 infected tumors HTLV-1 protein expression Other	No available information

OR = odds ratio

Decreased risk from human studies

Epidemiology Positive associations	Decreased risks in 3 cohort and 1 case-control study *Helicobacter pylori* positivity lower in HTLV-1 group compared with negative group
Human tissue Clonality % HTLV-1 infected tumors HTLV-1 protein expression Other	No available information

Preliminary Level of Evidence Summary

- Sufficient evidence for adult T-cell leukemia/lymphoma (ATLL)
  - Only HTLV-1 carriers develop ATLL
  - Higher risk with higher viral load
  - Monoclonal virus in tumors
  - 100% HBZ and 40% Tax expression
    - Tax promotes T-cell proliferation, growth, survival
    - HBZ maintains ATLL transformation and immortality
- Limited evidence for liver cancer
  - Positive, non-significant associations with HTLV-1 infection

Clarifications?

Peer Reviewer Comments

All sections: Comment on whether the information is clear and technically accurate and identify any information that should be added or deleted,

Properties, Detection and Human Exposure

- and whether adequate information is presented to document past and/or current human exposure.

Human Cancer Studies

- and provide any scientific criticisms of NTP's cancer assessment of the epidemiologic studies of exposure to the virus.

Mechanistic and Other Relevant Data

- and provide any scientific criticisms of the NTP's synthesis of these data assessing effects of the virus.

Level of Evidence Conclusion (Vote)

Sufficient evidence of carcinogenicity from studies in humans

- Cancer sites with sufficient evidence
  - Adult T-cell leukemia/lymphoma
- Cancer sites with limited evidence
  - Liver cancer

Preliminary Listing Recommendation (Vote)

HTLV-1

Human T-cell lymphotropic virus type 1 (HTLV-1) is *known to be a human carcinogen* based on sufficient evidence from studies in humans.

This conclusion is based on evidence from epidemiological and molecular studies, which show that HTLV-1 causes adult T-cell leukemia/lymphoma, and on supporting mechanistic data.

There is also limited evidence for an association with liver cancer.

Draft Substance Profile

- Contains NTP's preliminary recommendation of the listing status of the substance
- Summarizes the scientific information that is key to reaching a recommendation
- Provides information on properties, use, production, and exposure
- Provides information on existing federal regulations and guidelines

Peer Reviewer Comments

- Provide any new comments (e.g., not previously provided on the same facts or issues in the cancer hazard evaluation section) on whether the informtion on properties and detection, human exposure, cancer studies in humans and mechanistic data is clear and technically accurate.
- Comment on whether the substance profile highlights the information on cancer studies in humans and mechanistic data that are considered key to reaching the listing recommendation.