Draft RoC Monograph
Merkel Cell Polyomavirus

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Merkel Cell Polyomavirus (MCV)

Outline

Properties and exposure
Mechanistic information
Human cancer studies
Preliminary level of evidence summary
Properties and Significant U.S. Exposure

- Double stranded DNA virus, non-enveloped
- Part of normal skin flora, also detected in saliva
- Asymptomatic life-long infection in healthy individuals
- Although called Merkel cell virus, cellular origin of infection uncertain
- U.S. MCV seroprevalence rates reported as 20% in 1-5 yr olds, 35-50% in 10-15 yr olds, and 46-88% in adults
- Mode of transmission unknown – possibly through close contact of family members or from environmental sources
Assessment of Three Cancer Endpoints

- Merkel cell carcinoma
- Lung carcinoma
  - Inconsistent evidence, inadequate to assess.
- Chronic lymphocytic leukemia
  - Inconsistent evidence, inadequate to assess.
At least two mutations are needed to transform cells: integration of viral genome and large T antigen truncation.
MCV T-antigens transform cells *in vivo* and *in vitro*

- Expressed in MCV-infected tumors, and both antigens required to maintain tumor growth and survival
  - siRNA: reducing sT prevented proliferation of MCC; reducing sT and LT resulted in necrosis of MCV positive MCC
- MCV T antigens have oncogenic activity in transgenic mice
  - MCC derived truncated LT and sT antigens promoted skin neoplasias; sT expression alone sufficient for skin transformation
Truncated LT and sT Biological Effects

Antigen | Target | Biological Effect
--- | --- | ---
LT | pRb | Cell cycle progression
| Vam6p | Disruption of lysosomal clustering
| TLR9↓ | Disruption of immune signaling
| 4E-BP1 | Disregulation of CAP-dependent translation
| FBW7 | C-myc↑
| NEMO | Cyclin E↑

NF-κB mediated transcription↓

### Epidemiology

<table>
<thead>
<tr>
<th>Studies with positive associations or dose-response</th>
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<tbody>
<tr>
<td>21 case-series (716 MCV/855 MCC cases)</td>
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<tr>
<td>3/3 case-control studies; moderate to high statistically significant OR</td>
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<tr>
<td>1 nested case-control study – statistically significant increase in risk in females but only modest non-significant risk in males</td>
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### Human tissue

<table>
<thead>
<tr>
<th>Clonality</th>
<th>Monoclonal</th>
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<tr>
<td>% MCV-infected tumors</td>
<td>&gt;80% of MCC</td>
</tr>
<tr>
<td>MCV protein expression</td>
<td>Truncated Large T (LT) 75% of MCC</td>
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<tr>
<td></td>
<td>Small T (sT) antigen 92% of MCC</td>
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OR = odds ratio.
• Sufficient evidence for Merkel cell carcinoma
  – Moderate to high significant ORs in 3/3 case-control studies
  – Monoclonal integration
  – Express sT and truncated LT antigens

• Key mechanistic studies
  – Truncated LT and sT required to maintain growth and survival of human tumors
  – MCV T antigens have oncogenic activity in transgenic mice
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
  - Merkel cell carcinoma
Merkel cell polyomavirus (MCV) is known to be a human carcinogen based on sufficient evidence from studies in humans.

This conclusion is based on evidence from epidemiological, clinical, and molecular studies, which show that MCV causes Merkel cell carcinoma, and on supporting mechanistic data.
• 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 information 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.