

# From devils to jobs: tracking neuroendocrine tumors

Gary A. Clawson

Gittlen Cancer Research Foundation, and the Departments of Pathology & Biochemistry and Molecular Biology, Hershey Medical Center, Pennsylvania State University, Hershey, PA 17033, USA

Corresponding to: Gary A Clawson, Ph.D, M.D. Gittlen Cancer Research Foundation, and the Departments of Pathology & Biochemistry and Molecular Biology, Hershey Medical Center, Pennsylvania State University, Hershey, PA 17033, USA. Email: gac4@psu.edu.



Submitted Jan 15, 2013. Accepted for publication Feb 22, 2013.

doi: 10.3978/j.issn.2218-676X.2013.02.05

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Neuroendocrine tumors (NETs) are a diverse group of cancers, increasing in frequency, which can arise virtually anywhere in the body from cells of both the endocrine and nervous systems. Even given their diversity, NETs generally share common histologic features, and most (up to 85% of non-incident NETs) are “functional” in the sense that they produce hormones. Most clinically apparent NETs arise in the intestine or lungs, and are often grouped into foregut (including pancreas and lung), midgut, and hindgut tumors. Of the gastroenteropancreatic tumors, carcinoids (oddly named because they grew slowly and were thought to only be “cancer-like”) comprise ~2/3, while pancreatic endocrine tumors comprise the remaining ~1/3. Carcinoids are surprisingly frequent and are often discovered in the intestine during surgery for other indications, and a high frequency of incidental pancreatic NETs can be found at autopsy (1). NETs have achieved notoriety of late, both because their incidence is increasing [for example, (2)] and by afflicting such high profile people as Apple’s founder Steve Jobs. Diagnosis and/or staging often employs somatostatin-receptor scintigraphy (3,4). Although surgery is the only curative therapy, a variety of other therapies are available for patients with advanced disease, for palliation and/or relief of symptoms related to tumor size, including liver-directed treatments or administration of cytotoxic agents. A number of additional treatments are also being employed/explored, including use of somatostatin analogs (5,6), sunitinib [a tyrosine kinase inhibitor which targets angiogenesis pathways; (3)] , and Everolimus [which targets downstream effectors in the mTOR pathway, which is frequently mutated in NETs; (7)] for pancreatic NETs.

Adding to their notoriety is a bizarre “infectious” NET which is the cause of what is termed devil facial tumor

disease (DFTD), an infectious cancer which is decimating the Tasmanian devils. Transferred by biting, the infectious cells responsible for DFTD represent a Schwannoma (8,9), which is showing interesting patterns of evolution during transmission (10). DFTD appears to be transmitted as an allograft (11), based on natural history and serial transplantation studies, even though the Tasmanian devils can reject skin allografts (12). This NET is providing important insights into the role of MHC complex genes in immunosurveillance (13,14), as well as a potential model for the cancer stem cell process (11).

Following up on a report (15) that that insulinomas express EpCAM (epithelial cell adhesion molecule, Gene ID#4072), Khan and co-workers reported that the majority of NETs showed strong expression of EpCAM (16) (although why most NETs aberrantly express EpCAM is far from clear). This finding enabled them to employ standard CellSearch protocols to look for circulating tumor cells (CTCs) in patients with NETs, and the results were recently published in the *Journal of Clinical Oncology* (17). As with many other carcinomas, a relationship between number of CTCs and prognosis was found. In this study, the sample population consisted predominantly of midgut and pancreatic NETs, with smaller numbers of bronchopulmonary, unknown primaries, and hindgut NETs. Khan *et al.* (17) determined that the optimal prognostic threshold was essentially the presence of any CTCs; that is,  $\geq 1$  CTC/7.5 mL of blood (overall, 49% of patients had  $\geq 1$  CTC, *vs.* 42% with  $\geq 2$  CTCs). There are a number of interesting aspects of the data. For example, 47% of patients with midgut tumors had  $\geq 2$  CTCs *vs.* 24% of patients with pancreatic tumors, even though the group of patients with pancreatic tumors had an increased frequency of high grade lesions compared with the midgut cohort (36%

vs. 6%, respectively). Importantly, in grade 1 (83 patients) and grade 2 (63 patients) tumors, the presence of  $\geq 1$  CTCs was able to define a poor prognostic group for both progression free survival and for overall survival.

This report establishes the prognostic significance of the presence of CTCs in patients with clinical NETs in general, based on their aberrant expression of EpCAM. The numbers of cases were quite low for various subtypes (e.g., hindgut), so additional work is needed to extend these results to individual subtypes. However, these promising findings could well lead to stratification of patients for therapy, with the hope that earlier intervention could alter progression, as well as allow for monitoring early responses to therapies. Down the road, perhaps characterization of CTCs themselves can be accomplished.

It is important to note that within the CTC field in general, we don't really know who the "bad guys" are. That is, we don't yet know the nature of the CTCs which actually comprise the subset of CTCs that are capable of initiating metastasis (metastasis initiating cells, MICs). It is clear that in NETs, as with many other cancers (breast, colorectal, prostate, etc). CellSearch/EpCAM is certainly recognizing a surrogate marker of these MICs, but beyond that little is certain. Other than for convenience, there is little reason to exclude from consideration cells expressing CD45, an exclusion which CellSearch depends upon. Are the MICs cancer stem cells? Perhaps the NETs afflicting the endangered Tasmanian devils will provide some insight in this regard (11). What role do macrophage-tumor cell fusion hybrids (18-20) have in dissemination of tumor cells? Whatever the answer(s), CTCs should provide a valuable diagnostic/prognostic adjunct moving forward, as well as provide important insights into tumor biology and progression.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

*Conflicts of Interest:* The author has completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.3978/j.issn.2218-676X.2013.02.05>). The author has

no conflicts of interest to declare.

*Ethical Statement:* The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Cite this article as:** Clawson GA. From devils to jobs: tracking neuroendocrine tumors. *Transl Cancer Res* 2013;2(1):3-5. doi: 10.3978/j.issn.2218-676X.2013.02.05