# Conclusion – beyond RCC heterogeneity

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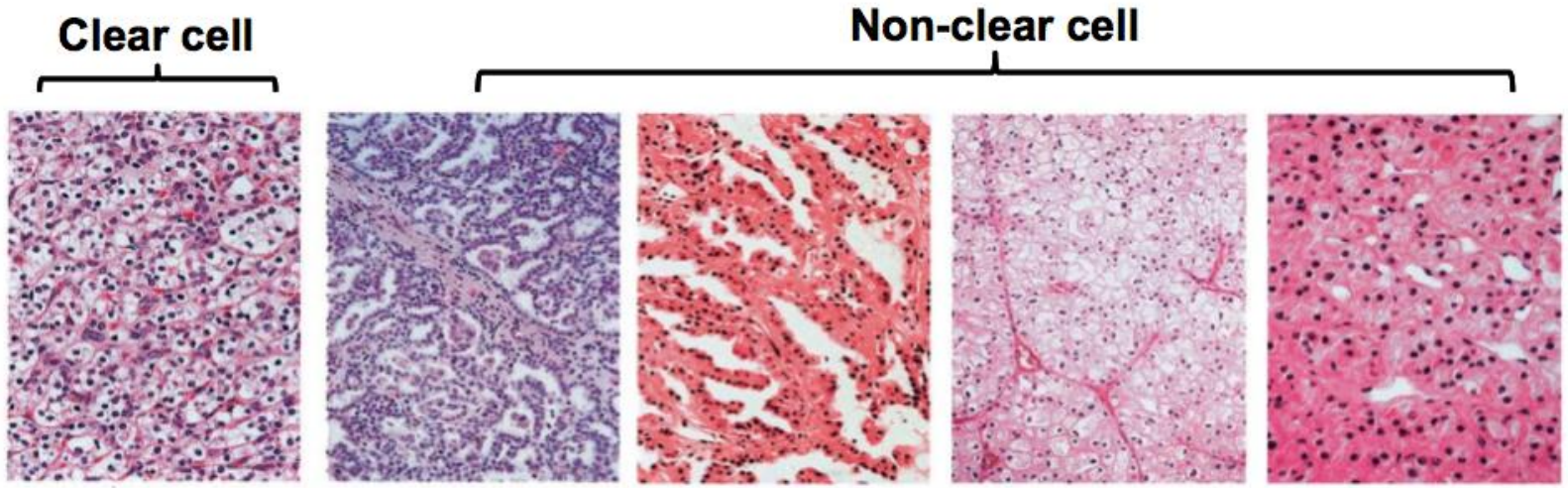
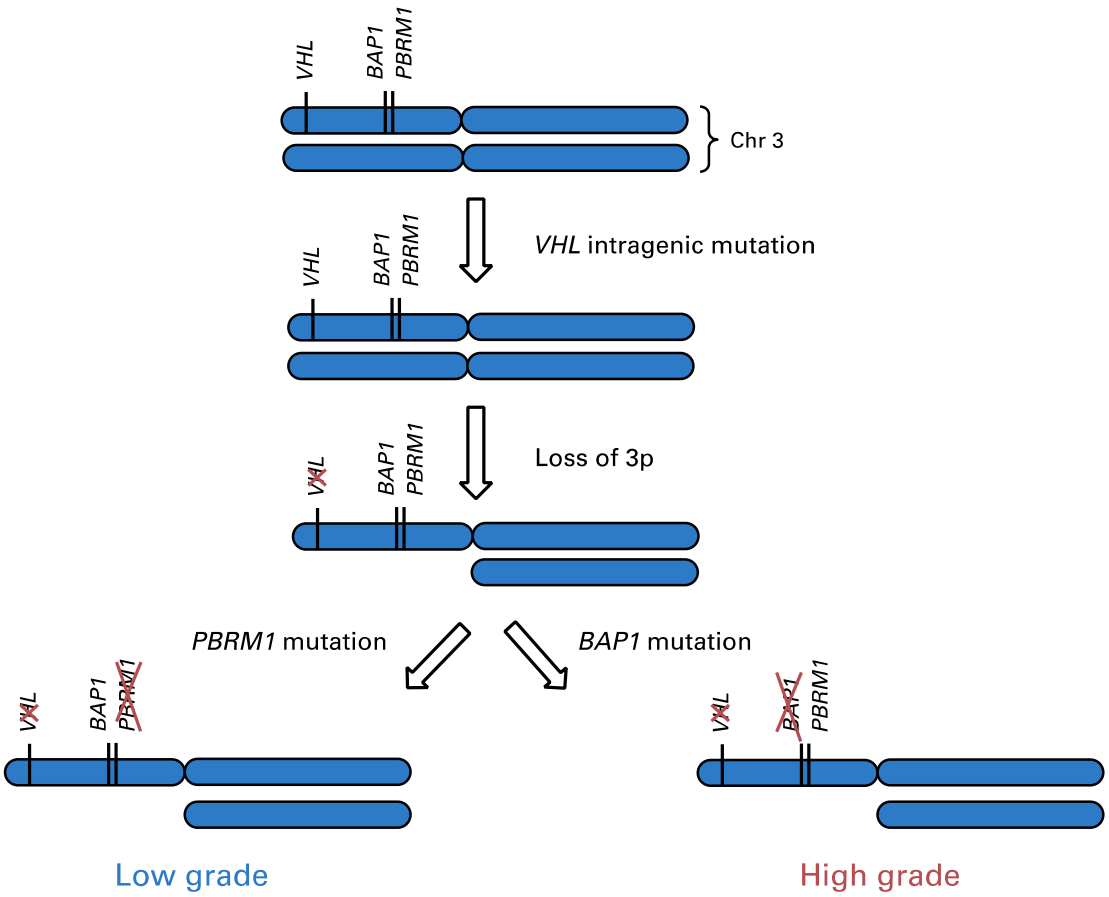
# RCC morphology and genetic alterations




BHD, Birt Hogg Dube; FH, fumarate hydratase.

Linehan WM et al. *J Urol.* 2003;170:2163-2172.

# Current view on RCC molecular evolution




Brugarolas, J. (2014). Molecular genetics of clear-cell renal cell carcinoma. Journal of Clinical Oncology, 32(18), 1968–1976. doi:10.1200/JCO.2012.45.2003

Clinical Cancer Research

# Tumor Genetic Analyses of Patients with Metastatic Renal Cell Carcinoma and Extended Benefit from mTOR Inhibitor Therapy

Martin H Voss, A Ari Hakimi, Can G Pham, et al.

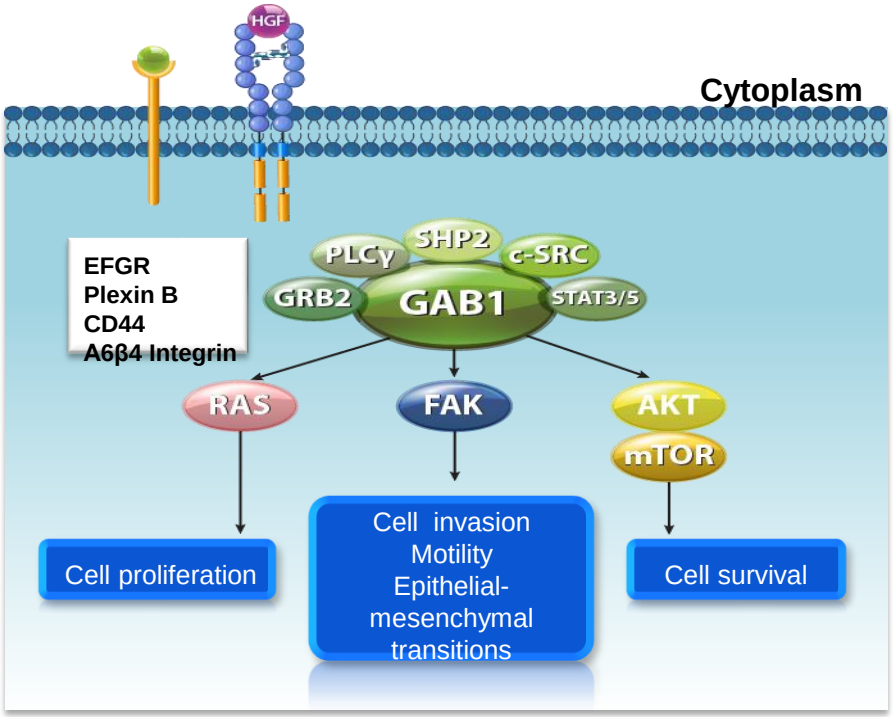
*Clin Cancer Res* Published OnlineFirst March 12, 2014.

| | Sex | Age | Histologic RCC subtype | MSKCC risk score[1,2] | Number of prior regimens | Treatment Duration on prior VEGF targeted agent [months] (agent) | Number of metastatic sites | Rapalog | Treatment Duration on rapalog [months] |
|---|---|---|---|---|---|---|---|---|---|
| **1** | F | 58 | clear | Int | 1 | 14 (sunitinib) | ≥3 | temsirolimus | 27 |
| **2** | F | 73 | clear | Int | 1 | 3 (sunitinib)[3] | 1 | temsirolimus | 34 |
| **3** | M | 66 | clear | Int | 2 | 5 (sunitinib) | ≥3 | everolimus | 20 |
| **4** | F | 60 | clear | Fav | 3 | 11 (sunitinib) | ≥3 | temsirolimus | 28 |
| **5** | F | 50 | unclassified | Fav | 1 | 2 (sunitinib) | ≥3 | temsirolimus | 45+ |

MSKCC: Memorial Sloan-Kettering Cancer Center Int: intermediate; Fav: favorable; VEGF: vascular endothelial growth factor;
[1] at the time of first rapalog dose; [2] Motzer, RJ et al., J Clin Oncol 1999;17:2580-2540; [3] discontinued due to treatment toxicity.

- mTOR or TSC mutations in 3/5 patients

# C-MET – a putative resistance mechanism during VEGF inhibition




- c-MET is a RTK that, after binding its ligand HGF, activates signalling pathways involved in cell proliferation, motility, migration and invasion[1,2]
- c-MET signalling is activated by tumour hypoxia and may be important in resistance to VEGF-targeted agents in cancer therapy[3]
- **Cabozantinib** and **Foretinib** inhibit MET and VEGFr-2[3]


1. Aftab DT et al. Clin Transl Oncol. 2011;13:703-9.
2. Organ SL. Ther Adv Med Oncol. 2011;3:S7-19.
3. Eder JP et al. Clin Cancer Res. 2009;15:2207-14.

# The Promise of Immunotherapy


The Clonal Evolution of Tumor Cell Populations

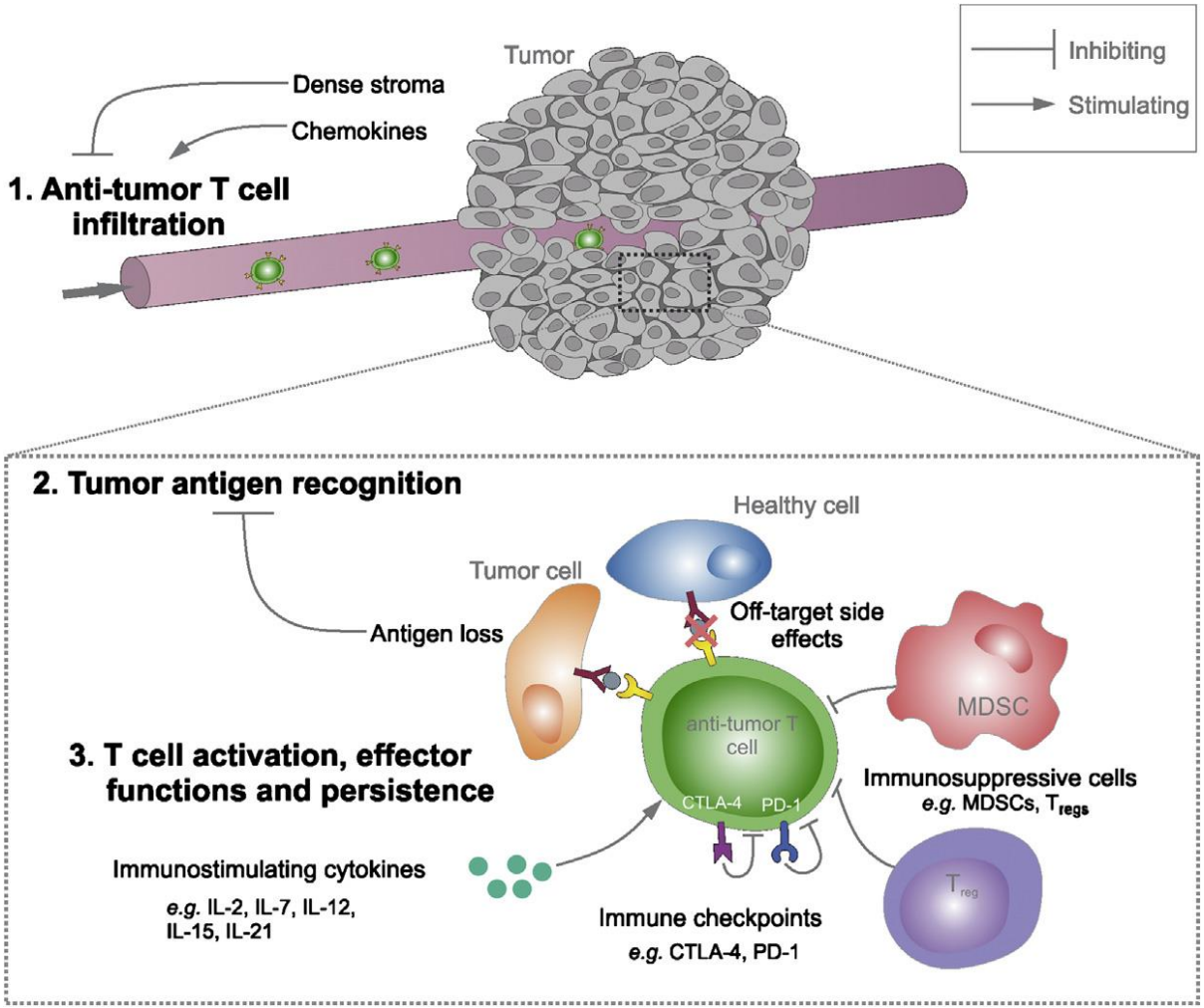
**Acquired genetic lability permits stepwise selection of variant sublines and underlies tumor progression.**

**Peter C. Nowell , 1976**

**"One may ultimately have to consider each advanced malignancy as an** individual therapeutic problem**….**Immunotherapy becomes a leading candidate for the easiest means of destroying the remainder of the neoplastic clone**...it is more** feasible **to produce specific cytotoxic antiserums or lymphocytes against a particular tumor than to design a specific chemotherapeutic agent for each neoplasm."**

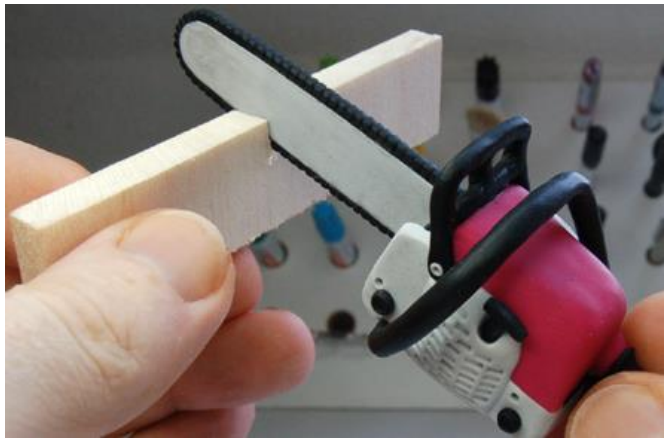
Courtesy of D. McDermott

# T-cells – the road to cure?




Wayteck et al. Cancer Letter 2014: 113-125

# Mission Lumberjack - the right tool for the task

# Individualization of therapy

- RCC is more heterogenous than initially thought
- Driving mutations are a chance to deliver substantial clinical benefit, but difficult to identify in RCC
- Immunooncology may overcome some of the hurdles of heterogeneity
- Developing effective immune-oncology regimens may help to individualize therapy in the future