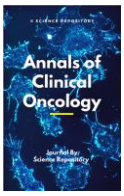

Available online at www.sciencerepository.org

Science Repository

## Comment/Analysis

# Deaminases and Why Mice Sometimes Lie in Immuno-Oncology Pre-Clinical Trials?

***Robyn A. Lindley[1,2] and Edward J. Steele[3,4*]***

[1]*GMDxCo Pty Ltd, Melbourne Vic, Australia*
[2]*Department of Clinical Pathology, Faculty of Medicine, Dentistry & Health Sciences, University of Melbourne*
[3]*CYO'Connor ERADE Village Foundation, 24 Genomics Rise, Piara Waters, 6112, Perth, Australia*
[4]*Melville Analytics Pty Ltd, Melbourne, Vic, Australia*

ARTICLE INFO

*Article history:*
Received: 2 March, 2019
Accepted: 17 March, 2019
Published: 30 April, 2019

Keywords:
*Cytosine and adenosine deaminase,*
*immuno-oncology pre-clinical trials*
*cancer progression*
*combinatorial association*
*somatic hypermutation*

ABSTRACT

There is now much evidence for the involvement of deaminase-mediated somatic mutagenesis during cancer progression. These developments lead us to reappraise the likely impact of AID/APOBEC and ADAR deaminases in human cancer progression with their expected lesser impact on somatic mutagenesis in mouse cancer model systems. The findings are important for pre-clinical trials of immune oncology (IO) drugs activating adaptive immune responses against tumor cells. Our conclusions are consistent with, and underline, recent recommendations by Decker and colleagues that IO pre-clinical trials should at least include therapies against spontaneous tumors in dogs. While the AID/APOBEC deaminase specificity repertoire in dogs is likely to be less than in humans, it will be far greater than in the mouse and thus more likely to better mimic dysregulated Ig like somatic hypermutation responses during cancer progression in humans.



## Abbreviations and Short Glossary

**ADAR,** Adenosine Deaminase that act on RNA, three main isoforms, ADAR1, ADAR2 and ADAR3 (ADAR3 is found in the brain only, and is a blocker with no demonstrable deaminase activity); **A**, adenosine; **AID**, activation induced cytidine deaminase, an APOBEC family member, initiating via C-to-U lesions in ssDNA of class switch recombination (CSR) and somatic hypermutation (SHM) processes at somatically rearranged Ig V(D)J gene loci, and known to activate cytidine mutagenic deamination during transcription in other somatic tissues, particularly in cancer; **APOBEC family**, generic abbreviation for the deoxyribonucleic acid, or dC-to-dU, deaminase family (APOBECs1,2,4 and human 3A/3B/ 3C/3D/3F/3G/3H) similar in DNA sequence to the "apolipoprotein B RNA editor" APOBEC1, and known to activate mutagenic cytidine deamination during transcription in somatic tissues, particularly in cancer; **AP**, an Abasic, or apurinic/apyrimidinic, site; **A-to-I**, adenosine-to-inosine RNA editing; **BER**, base excision repair; **C**, cytosine; **DBD**, deaminase binding domain of ADAR and AID/APOBEC enzymes; **Deaminase**, zinc-containing catalytic domain in ADAR and AID/APOBEC enzymes **H**, heavy chain of Ig; **I**, inosine; **Ig,** immunoglobulin; **Inf-DBD**, or inferred DBD that is consistent with a specific somatic mutation signature based on a C-or A-centered deamination 4-6+ nucleotide motif; **Ig-SHM-like** response, somatic mutation patterns resulting from uncorrected (or dysregulated) deaminase activity similar to that observed in Ig SHM; **L**, light chain of Ig**; IO,** immune oncology**; MHC,** major histocompatibility (complex) antigen presenting structures, MHC Class I and Class II**; MSH2-MSU6,** mutS homologue 2 and 6 mismatch repair heterodimer; **R**, Adenosine (A) or Guanine (G), purines; **S**, strong base pair involving Cytosine (C) or Guanine (G); **SHM**, somatic hypermutation; **SNV**, single nucleotide variation (somatic mutation); **T**, Thymine; **TCR**, T cell

**Correspondence to: Edward J Steele, Melville Analytics Pty Ltd, 708/ 14 Queens Rd, Melbourne, Vic, Australia; E-mail: e.j.steele@bigpond.com*


http://dx.doi.org/10.31487/j.ACO.2019.01.001

receptor; **TSM**, targeted somatic mutation: the process of transcription-linked targeting of genes by deaminases, and if unrepaired may result in a dominant type of mutation at a specific nucleotide motif (or Inf-DBD) and occurring at a particular codon reading frame position within the 3-N structure of the mutated codon; **U**, uracil; **UNG**, uracil DNA glycosylase; **W**, weak base pair involving A or U/T; **Y,** pyrimidines T/U or C.

**Mouse Cancer Models Often Fail**

Genetically defined inbred mouse strains have been an ideal pre-clinical trial vehicle for many years. The similarities in the basic anatomies and cellular architecture of the immune systems between the two mammals is very close. In cancer research, particularly immuno-oncology, there are at least two correlates between mice and men, which in their functional essence, are truly the same, namely:

a) The basic mechanisms of B and T cell adaptive immunity are very similar; in particular the mechanisms of immunoglobulin variable (V) to diversity (D) and joining (J) element rearrangements and the mechanism of somatic hypermutation, reviewed in Steele and the basic similarities between the immunogenetics of Ig and T cell receptors (TCRs, see text Murphy et al.) [1-3].

b) The basic identity between mice and men in the mechanisms of TCR recognition of foreign pathogen peptides presented in association with MHC Class I and Class II [3-5]. These fundamental attributes allowed the discovery and exploitation by James Allison and Tasuku Honjo of the murine CTLA-4 and PD-1 Checkpoint pathways which have resulted in significant immunotherapies in human cancer patients [6]. Indeed, pretty well all prior cancer chemotherapies have saved few if any patient lives [7, 8]. After years of failures of many different immunotherapies the Checkpoint therapies do indeed result in a significant proportion of patients cured of the disease [9, 10].

There have also been some spectacular failures in immunotherapies in human patients that seemed very promising in murine pre-clinical trials. Decker et al. focus attention on some of these failures [11]. A case in point is Sipuleucel-T (Provenge®, or APC8015) a putative dendritic cell (DC) vaccine. It is a cancer vaccine based on the patient's autologous DCs loaded with a fusion protein of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF). There is only limited overall survival (extra 4 months) and by 5 years post-administration, patients on Sipuleucel-T exhibit no survival probability over the placebo. Additionally, some 400 other dendritic cell vaccine trials carried out between 1995-2010 showed that Sipuleucel-T had no curative value in any patient [11]. Some other high-profile immuno-vaccine strategies that all failed in phase III clinical trials include GVAX vaccination, Melacine, CanVaxin, OncoPhage, Theratope, Bec2, and TRICOM (ProstVac and PanVac) [11]. The great bulk of the pre-clinical trials were in inbred mouse cancer models. Yet as Decker et al. aptly point out: "Given the sheer amount of positive preclinical and early clinical data required to justify the expense and risk of a phase III trial, how could this possibly have happened? [11]. Why did immuno- oncology vaccine therapies in particular, perform favorably in model systems yet so poorly in real-world studies? "

The most striking differences between inbred mouse models and the real world of human cancer are obvious when the list is clearly drawn up, Decker et al. [11].

- Mouse tumor models are highly contrived (genetically and biochemically). They are often chemically induced or passaged in syngeneic hosts. These are basic requirements for controlled experimentation, but tumors in man are spontaneous and could have a number of likely "first" causes. The longitudinal time dimensions are also important - "first cause to first clinical symptoms" can be precisely controlled in mice but are uncontrollable in human cancer sufferers.

- The mice being inbred lack all the "outbred" features of heterogeneous human populations with their myriad of protein and cell surface polymorphisms.

- The treatment environments of highly controlled specific pathogen-free (SPF) inbred mouse colonies are completely different to the uncontrolled variables in the best run cancer clinics.

The most important variable in our view is the lack of consideration of the somatic and germline genetic variability in mouse cancer models. Here we provide an overview of a growing body of work in understanding the links between deaminases and disease progression, and some core genomic differences between mice and men that furthers our understanding of “Why mice lie”.

**Deaminases from Yeast to Man**

It is now widely known that the dysregulated mutational activity of deaminases account for the majority of observed C-site and A-site mutations observed in most cancer genomes. So, while in the aggregate, a “driver gene” may take a mutational hit, there are many other dysregulated deaminations in the pre-cancerous stages. The patterns and numbers of these deaminase-mediated somatic mutations can allow a rational assessment of how active this off-target endogenous deaminase activity is in both apparently healthy tissue genomes and in progressing cancers.

Cytosine and adenosine deaminases are active in all metazoans as part of the first line Innate Immune response to pathogen invasion [12]. The deaminases are an evolutionarily evolved set of powerful mutagens designed to eliminate or attenuate the impact of invading pathogens such as viruses or bacteria. During an innate immune response involving deaminases, some host cell genes may also be mutated by the active deaminases during transcription. Both the number and type of deaminase genes and the specific target site activity within a deaminase family have all evolved to be different across species. There are also some differences in the deaminase genes expressed by different human populations. We have also shown that many genetic variations across human sub-populations are likely to be due to previous deaminase activity in humans over evolutionary time, Lindley and Hall [13].

In mammals the AID/APOBEC and ADAR deaminases are particularly important as their dysregulated activities can result in off-target immunoglobulin (Ig) like somatic hypermutation responses across the

genome resulting in cancer [14-16]. The mutagenic activity of C-site and A-site deaminase proteins become increasingly "uncontrolled" in somatic tissue and potentially target all expressed genes during transcription as human cancer progresses and displaying a clear maturation in the targeting specificity of their inferred deaminase binding domains (inf-DBDs), Lindley et al. [17]. This phenomenon of diversifying maturation in deaminase DBD target specificity has similarities with the maturation and diversification of antibody specificity and affinity during an antigen-driven adaptive immune response. These similarities are so striking we have now advanced a molecular model based on combinatorial association of the likely isoform proteins of the AID/APOBEC and ADAR deaminase families, Mamrot et al. [18]. Thus, deaminase homodimers are expected to be prominent in early cancers which on further somatic mutagenesis undergo dysregulation of Ig-SHM-like responses favoring the emergence of a range of novel AID/APOBEC and ADAR "heterodimers" displaying diversified differences in sequence motif specificities flanking the cystosine and adenosine targets [18].

What is important here is that, while all mammals express AID and APOBEC1 deaminases, there are a variety of forms of APOBEC3 genes in mammals. As well as the related APOBEC-like gene for activation induced cytidine deaminase (AID), there is a single APOBEC3 gene in rodents, cats, pigs, and sheep; there are two APOBEC3 genes in cows; there are three APOBEC3 genes in dogs and horses; and there are seven APOBEC3 genes in primates; APOBEC3B, APOBEC3D, APOBEC3F, APOBEC3G contain two deaminase binding domains, and differ from APOBEC1, AID, APOBEC3A, APOBEC3C and APOBEC3H which contain one deaminase binding domain [19].

Thus, the resulting potential AID/APOBEC diversity at C-site mutation targets will be far greater in humans than in mice. The potential AID/APOBEC combinatorial diversity in humans ( $\geq$ 110 DBD heterodimers) is discussed by us in Mamrot et al. [18]. In inbred mice, the number of sites potentially targeted by deaminases as a part of an innate immune response is further restricted by homozygosity so that there is a limited opportunity of a further polymorphic heterozygous contribution to form diverse DBD heterodimers (or higher multimers) during deaminase-mediated somatic mutagenesis in cancer progression [17, 20, 21]. C-site deamination is thus important as it leads to mutagenic G•U (uracils via C-to-U) and mutagenic G •T mispairs (thymine via C-to-T at 5MeCpG sites) which can mature to Abasic sites (AP), and then to single stranded DNA nicks by the action of AP endonucleases at Transcription Bubbles and in post transcription DNA repair (with 3'OH ends on the transcribed DNA strand) as discussed already , Lindley and Steele 2013, Steele and Lindley 2017, and which is largely confirmed by the molecular data of the Gearhart group [15, 22-24].

If we concede the key importance of the capacity for somatic mutagenesis during cancer progression as a core part of an innate immune response; and if we also concede a key causative role for dysregulated Ig-SHM-like responses of AID/APOBEC and ADAR deaminases causing C-site and A-site transition mutations (C-to-U/T and A-to-I/G) across the cancer genome; then we must now also concede that these somatic mutagenesis features of cancer progression are likely to be substantially restricted, or non-existent in inbred mouse cancer models.

**A Pre-Clinical Trial Solution?**

Thus, it is unlikely that there are any ideal non-human candidates for pre-clinical trials. Likewise, as we develop more immune targeting therapies, it is likely that there will be considerable variations in response across racial and regional genomic groups. So, what is the pre-clinical trial solution for initial testing of new immunotherapies?

Decker et al. advocate that dogs should be used in concert with inbred mice for all pre-clinical immunotherapy drug trials [11]. To paraphrase the recommendations:

Validation should take place in real-world physiological models prior to human clinical trials. The companion domestic canine population is very relevant because cancer is indeed the most common cause of death in pet dogs (about four million animals per year in the United States). The advantages are:

1. The dog cancer model is spontaneous, and thus relevant to real-world environmental and genetic stimuli.
2. Dogs, despite specific breeds, are outbred and more closely resemble the variability in human populations.
3. Dog immune systems are physiologically similar to humans. The animals share the same heterogeneous environments as their human masters exposed to a similar broad array of pathogens and commensals.
4. The clinic and field treatment environments are heterogeneous. Such heterogeneity in environmental conditions is rare in SPF animal houses.

It is therefore not surprising that Decker et al. have strongly recommended that the second IO test step in preclinical trials should be in dogs [11]. In our view the deaminase DBD diversity in canine populations will not be as great as for the humans. However, among the AID/APOBEC genes there will be at least 4 homodimer DBDs and 16 potential/hypothetical heterodimer DBDs in action late in canine cancer progression which includes the canine gene for AID [26]. Such diversity is clearly much greater than in inbred mice, and, with germline polymorphisms included in heterozygotes, the DBD diversity repertoire may be much greater than 20 different canine AID/APOBEC DBDs. Thus novel AID-associated heterodimer DBDs could initiate dysregulated Ig-SHM-like responses resulting in AID/APOBEC lesions opening the DNA to further mutagenic processes such as C-to-U at AID/APOBEC motifs (e.g. WRCW/RGYW), Abasic sites, AP endonuclease-mediated ssDNA nicks and error-prone DNA polymerases recruited via base excision repair (UNG) and mismatch repair (MSH2-MSH6) pathways [23-25].

We recognize that there are additional costs and possible pubic concern if canine pre-clinical trials become the ‘norm’. A further concern is that our canine friends may also ‘lie’ in pre-clinical trials.

The evolutionary conserved role of the ADAR1 p.150 isoform in murine and human innate immune systems is as a dsRNA sensor regulating activation of the cytosolic innate immune recognition differentiating responses to self and non-self (viral) dsRNAs [27, 28]. If we then assume the ADAR 1 and ADAR 2 isoforms play designated roles on nuclear and

cytosolic RNAs in normal cell physiology, we arrive at a limit of 30 potential ADAR heterodimer DBDs in all mammals serving conserved functional roles, Mamarot et al. [18]. The mouse ADAR1 is also known to behave as a tumor promoter in the same way ADAR1 is now viewed as an oncogene during progression in liver and gastric cancers in humans [29-31]. The consequences of functional motif diversity at ADAR targeted WA-sites could be far less than the deamination diversity at AID/APOBEC C-centered motifs, where AID normally plays the key role in initiating both Ig somatic hypermutation and class switch recombination [1, 2, 19, 25, 32]. Nevertheless, ADAR proteins can self-edit their ADAR mRNAs generating potential further DBD somatic diversity [33]. ADAR1 however, also generates A-to-I modifications in pre-mRNA substrates in the nucleus during transcription, [34, 35] and such RNA modifications are associated with the DNA mutations (WA-to-WG) at Ig SHM WA-hotspots in nascent dsRNA stem loops, Steele et al. [36].

## Concluding Comments

Thus, if we incorporate our recent knowledge on the role of deaminase mutagenic and regulatory activity in understanding cancer progression, and fundamental differences between the murine and human potential for deaminase targeting diversity, then we can better understand why 'mice lie'. The deaminases are a core component of innate immunity, and this, in our view, can now be a potential causal difference in the immune responses observed between mice and men during some clinical trials.

While we do not advocate the abolition of pre-clinical trials for therapies, we do support the idea that the pre-clinical testing phase for new cancer therapies can be improved to reflect our growing knowledge of the role of deaminases as part of an effective adaptive immune response. This may involve fully characterizing deaminase profile differences for the selected pre-clinical trial in animals, and humans. Characterization involving the identification of the relative expression levels of the different orthologous families of deaminase in both, and identifying genomic differences within each deaminase, will Improve our understanding the role of deaminases in pre-clinical trial animals and humans.

## Author Contributions

Robyn A. Lindley conceived of the key questions that allowed the proposed analysis to proceed and contributed to the joint writing of the draft manuscript with by Edward J. Steele.

## Conflict of Interest

The authors declare no conflict of interest.

## References


1. Steele EJ (2009) Mechanism of somatic hypermutation: Critical analysis of strand biased mutation signatures at A: T and G:C base pairs. *Molec Immunol 46*: 305-320. [Crossref]
2. Steele EJ (2016) Somatic hypermutation in immunity and cancer: critical analysis of strand-biased and codon-context mutation signatures. *DNA Repair (Amst)* 45: 1-24. [Crossref]
3. Murphy K, Weaver C, Mowat A, Be L, Chaplin D, et al. (2017) Janeway's Immunobiology 9th Edition, GS Garland Science, Taylor & Francis Group, New York and London.
4. Doherty PC, Blanden RV, Zinkernagel RM (1976) Specificity of virus-immune effector T cells for H-2K or H-2D compatible interactions: implications for H-antigen diversity. *Transplant Rev* 29: 89-124. [Crossref]
5. Zinkernagel RM, Doherty PC (1997) The discovery of MHC restriction. *Immunol Today* 18: 14-17. [Crossref]
6. Friedrich MJ (2019) Immunotherapy 2.0: Improving the response to Checkpoint Inhibitors. *JAMA* 321: 131-133. [Crossref]
7. Domingues B, Lopes JM, Soares P, Pópulo H (2018) Melanoma treatment in review. *Immunotargets Ther* 7: 35-49. [Crossref]
8. Ward WH, Farma JM (2017) (Editors) Cutaneous Melanoma: Etiology and Therapy. Codon Publications, Brisbane, Australia. [Crossref]
9. Larkin J, Chiarion Sileni V, Gonzalez R, Grob JJ, Cowey CL, et al. (2015) Combined Nivolumab and Ipilimumab or Monotherapy in untreated melanoma. *N Engl J Med* 373: 23-34. [Crossref]
10. Robert C, Ribas A, Hamid O, Daud A, Wolchok JD, et al. (2018) Durable complete response after discontinuation of pembrolizumab in patients with metastatic melanoma. *J Clin Oncol* 36: 1668-1674. [Crossref]
11. Decker WK, da Silva RF, Sanabria MH, Angelo LS, Guimarães F, et al. (2017) Cancer Immunotherapy: Historical perspective of a clinical revolution and emerging preclinical animal models. *Front Immunol* 8: 829. [Crossref]
12. Krishnan A, Iyer LM, Holland SJ, Boehm T, Aravind L (2018) Diversification of AID/APOBEC-like deaminases in metazoa: multiplicity of clades and widespread roles in immunity. *Proc Natl Acad Sci U S A* 115: E3201-E3210. [Crossref]
13. Lindley RA, Hall NE (2018) APOBEC and ADAR deaminases may cause many single nucleotide polymorphisms curated in the OMIM database. *Mutat Res* 810: 33-38. [Crossref]
14. Steele EJ, Lindley RA (2010) Somatic mutation patterns in non-lymphoid cancers resemble the strand biased somatic hypermutation spectra of antibody genes. *DNA Repair (Amst)* 9: 600-603. [Crossref]
15. Lindley RA, Steele EJ (2013) Critical analysis of strand-biased somatic mutation signatures in TP53 versus Ig genes, in genome - wide data and the etiology of cancer. *ISRN Genomics* 2013: 18.
16. Lindley RA (2013) The importance of codon context for understanding the Ig-like somatic hypermutation strand-biased patterns in TP53 mutations in breast cancer. *Cancer Genet* 5: 2619-2640. [Crossref]
17. Lindley RA, Humbert P, Larmer C, Akmeemana EH, Pendlebury PRR (2016) Association between targeted somatic mutation (TSM) signatures and HGS-OvCa progression. *Cancer Med* 5: 2629-2640. [Crossref]
18. Mamrot J, Balachandran S, Steele EJ, Lindley RA (2019) Molecular model linking Th2 polarized M2 Tumor Associated Macrophages with deaminase-mediated cancer progression mutation signatures. *Scand J Immunol* 25: e12760. [Crossref]

19. Smith HC, Bennett RP, Kizilyer A, McDougall WM, Prohaska KM (2012) Functions and regulation of the APOBEC family of proteins. *Semin Cell Dev Biol* 23: 258-268. [Crossref]
20. Harari A, Ooms M, Mulder LC, Simon V (2009) Polymorphisms and splice variants influence the antiretroviral activity of human APOBEC3H. *J Virol* 83: 295-303. [Crossref]
21. Gourraud PA, Karaouni A, Woo JM, Schmidt T, Oksenberg JR, et al. (2011) APOBEC3H haplotypes and HIV-1 pro-viral vif DNA sequence diversity in early untreated human immunodeficiency virus-1 infection. *Hum Immunol* 72: 207-212. [Crossref]
22. Steele EJ, Lindley RA (2017) ADAR deaminase A-to-I editing of DNA and RNA moieties of RNA: DNA hybrids has implications for the mechanism of Ig somatic hypermutation. *DNA Repair (Amst)* 55: 1-6. [Crossref]
23. Maul RW, Saribasak H, Martomo SA, McClure RL, Yang W, et al. (2011) Uracil residues dependent on the deaminase AID in immunoglobulin gene variable and switch regions. *Nat Immunol* 12: 70-76. [Crossref]
24. Zanotti KJ, Maul RW, Yang W, Gearhart PJ (2019) DNA Breaks in Ig V Regions are predominantly single stranded and are generated by UNG and MSH6 DNA Repair Pathways. *J Immunol* 202: 1573-1581. [Crossref]
25. Maul RW, Gearhart PJ (2010) AID and somatic hypermutation. *Adv Immunol* 105: 159-191. [Crossref]
26. Ohmori K, Maeda S, Okayama T, Masuda K, Ohno K, et al. (2004) Molecular cloning of canine activation-induced cytidine deaminase (AID) cDNA and its expression in normal tissues. *J Vet Med Sci* 66:739-741. [Crossref]
27. Liddicoat BJ, PiskolR, Chalk AM, Ramaswami G, Higuchi M, et al. (2015) RNA editing by ADAR1 prevents MDA5 sensing of endogenous dsRNA as nonself. *Science* 349: 1115-1120. [Crossref]
28. Samuel CE (2019) Adenosine deaminase acting on RNA (ADAR1), a suppressor of double-stranded RNA–triggered innate immune responses. *J Biol Chem* 294: 1710-1720. [Crossref]
29. Ishizuka JJ, Manguso RT, Cheruiyot CK, Bi K, Panda A, et al. (2018) Loss of ADAR1 in tumours overcomes resistance to immune checkpoint blockade. *Nature* 565: 43-48. [Crossref]
30. Chan TH, Lin CH, Qi L, Fei J, Li Y, et al. (2014) A disrupted RNA editing balance mediated by ADARs (Adenosine Deaminases that act on RNA) in human hepatocellular carcinoma. *Gut* 63: 832-843. [Crossref]
31. Chan THM, Qamra A, Tan KT, Guo J, Yang H, et al. (2016) ADAR-mediated RNA editing predicts progression and prognosis of gastric cancer. *Gastroenterology* 151: 637-650. [Crossref]
32. Di Noia JM, Neuberger MS (2007) Molecular mechanisms of somatic hypermutation. *Annu Rev Biochem* 76: 1-22. [Crossref]
33. Farajollahi SI, Maas S (2010) Molecular diversity through RNA editing: a balancing act. *Trends Genet* 26: 221-230. [Crossref]
34. Herbert A, Alfken J, Kim YG, Mian IS, Nishikura K, et al. (1997) A Z-binding domain present in the human editing enzyme, double-stranded RNA adenosine deaminase. *Proc Natl Acad Sci* 94: 8421-8426.
35. Herbert A, Rich A (2001) The role of binding domains for dsRNA and Z-DNA in the in vivo editing of minimal substrates by ADAR1. *Proc Natl Acad Sci USA* 98: 12132-12137. [Crossref]
36. Steele EJ, Lindley RA, Wen J, Weiller GF (2006) Computational analyses show A-to-G mutations correlate with nascent mRNA hairpins at somatic hypermutation hot- spots. *DNA Repair (Amst)* 5: 1346-1363. [Crossref]