1. Objective
This work aims to explain how β-catenin is stabilized upon activation of the Wnt pathway and also its implication in the colon cancer development.

2. β-catenin in context
β-catenin is an integral structural component of cadherin-based adherent junctions, and the key nuclear effector of canonical Wnt signalling in the nucleus. Imbalance in the structural and signalling properties of β-catenin often results in disease and deregulated growth connected to cancer and metastasis.

3. The canonical Wnt pathway and the different components implicated
Absence of ligand: β-catenin that is not bound to the cytosolic tail of cadherin proteins becomes bound by a degradation complex containing APC, axin, GSK3 and CK1. In this complex, β-catenin is phosphorylated by GSK3 triggering its ubiquitination and degradation in proteasomes.

Presence of ligand: Wnt binds to Frizzled and LRP, resulting in the recruitment of the degradation complex to the plasma membrane. Then β-catenin can accumulate and translocate to the nucleus. Once is in the nucleus, β-catenin binds to LEF1/TCF and acts as a coactivator to stimulate the transcription of Wnt target genes.

4. Intestinal Crypts and the involvement of the Wnt pathway in their development and maintenance
The epithelium of colon is organized in crypts and displays a remarkable self-renewal rate. This is an active proliferation that is confined to the crypts. Resident stem cells are located to the crypt bottom and they give rise to transit-amplifying (TA) cells which move upward towards the crypt border. During this migration, these TA cells begin to differentiate and subsequently exit the crypt.

In the intestine, two models of intestinal stem cell identity have been formulated: the stem cell zone model and the +4 model.

The stem cell zone model
• In the crypt base there are crypt base columnar cells (CBCs)

+4 model
• Rare DNA-label-retaining cells (LRCs) reside above the Paneth cells (+4 position)

5. Colon Cancer
More than 95% of colon cancers are sporadic and their origin is due to Wnt effectors’ mutations. The inactivation of APC leads to an accumulation of free β-catenin and this can be observed in about 80% of sporadic colon carcinomas. The rest of sporadic colon carcinomas carry wild-type APC alleles, but some of these carry point mutations in the gene which encodes for β-catenin or mutations in Axin2. In some cases, the APC gene promoter is hypermethylated and rendered inactive. These mutations will lead to an accumulation of β-catenin too.

The accumulation of β-catenin in enterocyte precursor due to the mutations explained above, causes to the enterocyte precursor to retain a stem cell-like phenotype, which excludes it from migration out of the crypts. This leads to the accumulation of large numbers of relatively undifferentiated cells in a colonic crypt, which eventually form adenomatous polyps.

6. Therapy
Nowadays there isn’t a cure for colon cancer. However, there are some therapies that can help to treat this cancer:

Vitamin D
• Calcitriol is the most active vitamin D metabolite and inhibits Wnt-β-catenin signaling.

Celecobix
• is a selective COX-2 and COX-2 inhibition leads to an increase in β-catenin’s phosphorylation.

Resveratrol
• is a long-term inhibitor of COX-2 and COX-2 inhibition leads to an increase in phosphorylation of β-catenin. Also, resveratrol reduces ornithine decarboxylase expression and is a moderately selective inhibitor of COX-1.

7. Conclusions
β-catenin has different roles in the cell and one of them is its implication in the Wnt pathway. This pathway is very important because its correct functionality is required for the development and maintenance of the intestinal crypts. However, if an alteration in a component of this pathway is presented, then there will be an up-regulation because the correct function won’t be possible and an alteration in the crypts will be observed and this will lead to inductive tumours.

Nowadays, a pharmacologic treatment for colon cancer does not exist. Thus, it is important to know exactly the molecular mechanism of the Wnt pathway.

8. References