



Patient Report

Drugs & PJS

A Report by
Stephanie Sugars

This report is focused on drugs. First, I'll disclose my conflict of interest (not drug company funding): I'm very cautious about drugs. And x-rays, surgery, hospitals, etc. Since I've had complications from them and met many others who have, I am super-sensitized to the limitations of modern medicine. Experience has taught me that there are very few magic bullets in medicine. The drugs, surgeries, etc. may fix one problem but often cause others. And if I am cautious about the established procedures, I'm biased against genetic medicine, especially germline genetic engineering.

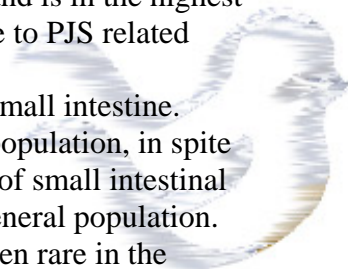
Thus far, there've been very few drugs associated with PJS. For surgery there are anesthesia and pain killers. For cancer there is also chemotherapy and the many drugs that support it.

Soon people with PJS may face decisions about drugs to reduce both polyps and cancer risk. As I've reported previously, researchers around the world are exploring the PJS mystery. Each group has different interests and working models. Some do mice: Japan, Finland, Germany, California and Boston in USA. Others do flies: Cambridge, UK. Another group in Boston, USA, with an NCI grant to research apoptosis and LKB1 (the PJS gene product) wrote a review of the research to-date.¹

Other researchers are working on blood, polyps and cancers from PJS folks to find both genetic mutations and the characteristics of PJS polyps and cancers. Recent reports from some of these groups point toward possible drug interventions for PJS polyps and cancers.

Mutations of LKB1/STK11 on chromosome 19p13.3 lead to PJS in most PJS folks. There is likely a second mutation site, which won't be explored here. Anyway, researchers are very interested in LKB1/STK11 for many reasons. Here are a few:

- It's highly conserved not just in humans, but mice, frogs, flies and even worms, which means that it's important to life.
- It plays a function in embryonic development. Mice with a double LKB1/STK11 mutation don't survive gestation. Human embryonic tissue expresses high levels of it.
- It is widely disbursed throughout the human body and is in the highest concentrations in areas of the body especially prone to PJS related cancers (testis, small intestine, pancreas, ovary).²
- It appears to have a cancer protective effect in the small intestine. Cancer of the small intestine is rare in the general population, in spite of the rapid turnover of cells in that area.¹ The risk of small intestinal cancer for PJS folks is over 500 times that of the general population.
- The polyps, tumors and cancers in PJS folks are often rare in the general population: small bowel polyps, hamartomatous polyps, sex cord tumors, cervical minimal deviation adenocarcinoma. Even the more common cancers like colon, breast and pancreatic often have odd signatures like early age of onset, unusual pathological features and bi-laterality.



- Researchers also study LKB1/STK11 expression in the tumors of non-PJS folks, to understand whether it plays a part in sporadic (non-PJS originated) tumors. Most studies don't show a strong link between LKB1/STK11 and tumors of non-PJS folks.
- Another mystery of LKB1/STK11 is that its inactivation (mutation) leads to polyps and cancers. STK11 stands for serine-threonine kinase. It is the first known instance that an inactivation of a kinase leads to cancer. In many cancers a kinase overexpression leads to cancer. Drug research into targeted therapies for cancer usually focus on suppressing or inhibiting overexpressed proteins and kinases.
- When functional LKB1/STK11 is introduced to cancer cells that don't express it, it can suppress cell growth in the laboratory.³ I'm unsure whether introducing functional LKB1/STK11 is possible in humans. Would it be a drug therapy or a genetic therapy? Would anyone find it worthwhile to develop this for PJS folks?

While researchers around the world explore LKB1/STK11 and PJS from different angles, we PJS folks wonder about a cure for PJS.

A recent article by our members, Dr. Tom McGarrity and Dr. Chris Amos and others, explores Cox-2 overexpression in PJS polyps.⁴ A previous article found that Cox-2 is highly up-regulated in the polyps of PJS mice and humans.⁵ That article led to a clinical trial in Finland that a group member has written about. Participants took 200 mg of celebra two times daily for six months with scopes performed at the beginning and end of the study.

The new article confirms that Cox-2 is overexpressed in PJS polyps and suggests that Cox-2 inhibitors might be used to reduce PJS polyps. These drugs are already used to reduce polyps in another hereditary polyposis syndrome: FAP or familial adenomatous polyposis. I've written reports about Cox-2 expression and inhibitors for this group. A good, comprehensive article about Cox-2 inhibition in cancer is available free online.⁶

It is my hope that good, well-designed clinical trials on Cox-2 inhibitors in PJS are developed in the USA and other countries and that some of our members will participate in them. What is found in those trials will affect treatment options for all PJS folks. Drugs may be in our future. Their promise for cure, reduction of polyps and cancer chemoprevention are yet to be determined. Yet, our participation in clinical trials could be vital in developing drugs for PJS.

Remember: I am a patient, not a medical professional. I am not giving medical advice, but reporting on what I've read. You are welcome to share this letter with your physician. And I am happy to provide more references on the other research projects.

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³Boudeau J, Kieloch A, Alessi DR, Stella A, Guanti G, Resta N. *Functional analysis of LKB1/STK11 mutants and two aberrant isoforms found in Peutz-Jeghers Syndrome patients*. Hum Mutat. 2003 Feb;21(2):172.
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⁵Rossi DJ, Ylikorkala A, Korsisaari N, Salovaara R, Luukko K, Launonen V, Henkemeyer M, Ristimaki A, Aaltonen LA, Makela TP. *Induction of cyclooxygenase-2 in a mouse model of Peutz-Jeghers polyposis*. Proc Natl Acad Sci U S A. 2002 Sep 17;99(19):12327-32.
PMID: 12218179 [PubMed - indexed for MEDLINE]
Full text Available for free at <http://www.ncbi.nlm.nih.gov/PubMed/>

⁶Suphat Subongkot, Pharm.D., David Frame, Pharm.D., William Leslie, M.D., Deborah Drajer, Pharm.D. *Selective Cyclooxygenase-2 Inhibition: A Target in Cancer Prevention and Treatment Pharmacotherapy*
<http://www.medscape.com/viewarticle/448279>

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