Necessary and sufficient conditions for an anticancer “magic bullet”

Vladimir Pak
Constab Pharmaceutical Inc., MaRS Centre, Toronto, Ontario, Canada.
Sponsored by the Ministry of Research and Innovation Ontario and Going Global S & T Program, Canada.

1 Background
Cancer is the leading proliferative-programmed cell death (apoptosis) imbalance. The balance could be fixed by the selective stimulation of apoptosis, but the clinical activation of apoptosis in a living tissue, traditional anticancer drugs mostly suppress proliferation (1, 2). In 1947, plane passenger traffic rate and in 2016, car traffic rate equal to the increase of cancer incidence rate (3). Coronary arteries become atherosclerotic, on the other hand, cancer cells accumulate mutations, including crucial mutations in apoptosis system. Cytopathic T lymphocytes (CTL) are the advantage of cell death in apoptosis system and acting “poison” of the dynamic dominance by apoptosis. We tend to follow Nature’s system principle of CTL.

1. Specifically identify cancer cells.
2. Use perforin for the internalization of granzyme B.
3. Use granzyme B as an effective agent to induce apoptosis

Alpha-fetoprotein (AFP) is a human embryonic marker (4), which has its highly specific receptors (AFPR) in the majority of cancer cells (5, 6). AFP was used for targeted delivery and internalization (7) of different agents into the cancer cells (8). We have selected apoptosis inducer (AI) to target metastasis. Injections of apoptosis inducer into a “cancer mass” of all that is should be more than 95% of cancer cells (9) and is responsible for multi-drug resistance (10). By the way (AI as well as CTL), cancers p(0) dependent MDR of cancer cells (11). Using selected AI and targeted delivery technology, based on highly selected AFP tumor we have constructed our drug candidate - Aimpila and investigated its properties in vitro and in vivo trials.

2 Methods

Mouse study: 10 mice in control or Aimpila groups after 20,000 P-388 tumor cells subcutaneous inoculation on day 0 were every day gavaged for the next 20 days with 0.3 mg of Aimpila in an oral capsule, twice a day for 8 weeks.

Human study: Patients aged 45-65, ECOG (Eastern Cooperative Oncology Group) performance status was 0, the median age was 56 years (range 45-65), and the median time from previous treatment failure was 9.0 months (range 1-20). CT scans were performed before and after treatment. CT-scanning had shown that 6 out of 12 mCRC patients (50%) had responded to suboptimal monotherapy with Aimpila™ capsules (7).

3 Results

1. Growth of animals with Aimpila. Growing 21 days has lead to a 85% reduction of tumor growth (Fig. 2 and 3) compared to untreated control mice (Fig. 1). The maximum rate was at day 7 of treatment (Fig. 2). More than 70% of tumor mass were non-proliferative before and after treatment.

2. CT scanning had shown that 6 out of 12 mCRC patients (50%) had responded to suboptimal monotherapy with Aimpila™ capsules (7).

4 Discussion

Aimpila fits necessary and sufficient conditions for an anticancer “magic bullet”:
- Specifically delivers AI to cancer cell
- Internalizes AI into cancer cell
- Use effective AI, acting “downstream” of mutated apoptosis element

 specification/efficacy ratio and are thus causing side effects. Moreover, they do not overcome multi-drug resistance (MDR). Apoptosis recycles but the direct activation of apoptosis is a better idea. Traditional anticancer drugs mainly suppress proliferation (1)(Fig. 2), have poor selection to their targets and are not efficient in low drug dosages (3). Aimpila meets the criteria for the “magic bullet” properties because:

- It is highly selective to AFPR-positive cancer cells
- It is internalized through receptor-mediated endocytosis
- It has high efficacy due to the mechanism of action of the Apoptosis Inducer (AI = mitochondria toxins)

5 Conclusion

Aimpila meets the criteria for the “magic bullet” properties because:
- It is highly selective to AFPR-positive cancer cells
- It is internalized through receptor-mediated endocytosis
- It has high efficacy due to the mechanism of action of the Apoptosis Inducer (AI = mitochondria toxins)

6 References