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In use of Olaparib for ovarian cancer: understanding from pathogenesis, target corroboration, discovering process and treatment techanism

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Abstract. The second most prevalent gynecologic cancer, ovarian cancer has a poor prognosis, is difficult to diagnose, and has a high mortality. EOC (epithelial ovarian cancer) is the most common subtype. PARP inhibitor has so far been approved by FDA, and used for target therapy of epithelial ovarian cancer worldwide. This article based on lots of literature research, reviews studies of ovarian cancer pathogenesis, target corroboration, Olaparib discovering process and treatment mechanism. Somatic sequence mutation occupies a prominent position in the pathogenesis of ovarian cancer. Type I ovarian cancer behave PIK3CA KRAS, BRAF, PTEN, and CTNNB1 sequence mutation. Type II ovarian cancers exhibit TP53 and BRCA1/2 sequence mutation. Angiogenesis, TP53, and PARP are studies in target therapy of ovarian cancer. PARP is regarded as ideal target, Olaparib is the first PARP inhibitors. Preventing PARP works in DNA damage repairing in BRCA mutation ovarian cancer cells causing cell death preferentially are confirmed as the therapeutic mechanism of Olaparib (PARP inhibitor), in therapy of ovarian cancer.

Keywords: Olaparib, ovarian cancer, pathogenesis, TP53, angiogenesis, PARP.

1. Introduction

Generally, indications of Olaparib can be summarized as maintanance therapy of recurrent fallopian tube cancer (FTC), primary peritoneal cancer (PPC), breast cancer (BC), and epithelial ovarian cancer (EOC).

According to cancer statistics of Centers for Disease Control and Prevention United States (CDC), ovarian cancer is regarded as the second most frequent gynecologic malignancy in the United States. At the same time, ovarian cancer is so difficult to diagnose that large probability patients appear in stage III or IV, and causes higher mortality rate, approximate 70%. Besides ovarian cancer behaves poor prognosis.

The three main categories of ovarian carcinoma are epithelial, germ cell, and specialized stromal cell tumors. Among three large groups, EOC occupies 85% to 95%. Emergency of dualistic model of carcinogenesis changed the classification of EOC, and EOC subtypes are divided into Type Ⅰ and

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Type Ⅱ. [1]

In accordance with results of TCGA, pathogenesis of ovarian cancer is concluded. Type Ⅰ ovarian cancer happens because sequence mutations have taken place within somatic cells, including CTNNB1, PTEN, PIK3CA, BRAF and KRAS. However, these sequences give a major function in regulating different signaling pathway, leading to cell signaling disorders, cell proliferation and cancer. Same as type Ⅰ ovarian cancer, type Ⅱ ovarian cancer takes place also because of somatic sequence mutation. What is different from type Ⅰ ovarian cancer is the type of genes, including TP53, BRCA1/2.

Since the heterogeneity of ovarian cancer is found, targets therapy of ovarian cancer is regarded as more effective and less toxic strategy. Studies of targets therapy of ovarian cancer gradually developed. Currently, several effective targets have been identified, including TP53, angiogenesis, and PARP. Due to highest specificity, excellent therapeutic effect, lots of research achievements, PARP inhibitors got a lot of attention. Olaparib is the first PARP inhibitor studies.

On the basis of FDA approval documents of Olaparib tablets (Lynpara Astra Zeneca), Olaparib can be used to BRCA-mutated (gBRCAm) advanced ovarian cancer, classified into High-grade serous ovarian carcinoma (HGSOC).

Olaparib has so far been used to treat over 40,000 people with cancer worldwide. Discovery of Olaparib derive from an anti-cancer drugs project applied by Steve. After focusing on DNA damaging studies, Steve discovered defects in DNA repair could be exploited in 1997. Therefore, KuDOS are set up by Steve to do more research for foregoing finding of Steve, and Olaparib was discovered by KuDOS. Due to insufficient funds，Olaparib was sold to AstraZeneca , thus finishing clinical studies and getting approval.

In 2014, FDA approved that Olaparib can be used for the cure of gBRCAm ovarian cancer in the last stage after third-line or high-line chemotherapy. Of the same year, combining data of trial of phase II, EMA indicates the use of HGSOC and Olaparib is not less than 8 circles after a session of platinum-based drugs, when the size of tumour shrinks or disappears totally [2]. In 2017 ,Olaparib maintenance treatment in recurrent PPC EOC, and FTC were approved. In 2018, Olaparib got approval of FDA for gBRCA metastatic breast cancer. In 2019-2022, maintenance therapy for gBRCAm metastatic pancreatic cancer and HER2 negative adjuvant therapy for incipient-risk early-stage breast cancer are approved for early or advanced stages [3, 4].

PARP 1, PARP 2, BRCA 1, and BRCA2 play important role in DNA damage repairing. PARP 2, BRCA 1/2 work in repairing double-strand breaks of DNA by the HRR pathway. PARP 1 can repairs SSB, which can cause double strand breaks if are not repaired and replicate. PARP inhibitor can prevent PARP1/2 from acting, prevent repairing DNA damaging. Thus, DNA breaks lack of efficiently repaired, resulting in the death of the cancer cells. However, if PARP1/2 are prevented, Under the influence of BRCA1/2 DNA damaging still can be repaired. Due to BRCA-mutated (gBRCAm) ovarian cancer lack of the influence of BRCA1/2, under the influence of PARP inhibitor Olaparib, DNA damaging lack of repair, thus to achieve the therapeutic effect.

2. Pathogenesis of ovarian cancer

Initially, Fathalla proposed "incessant ovulation" hypothesis, and proves that EOC were derived from the ovarian surface epithelium (OSE) [5]. The hypothesis indicates that frequent and incessant ovulation cause DNA damage of epithelial cell of ovary, and repairing DNA damage need DNA synthesis, which can increase mutation rate. In 2001, histological specimens from 12 female patients who had been determined as genetic susceptibility to ovarian cancer as samples, the existence of tumor lesions was scored, positive of germline BRCA1 mutation was shown in 7 samples, indicating the existence of small atypic lesions in the fallopian tubes [6].

Although dualistic model divides ovarian cancer into two subtypes, ype Ⅰ and type Ⅱ, additionally each type includes many subtypes. Due to poor diagnosis measure, majority ovarian cancers are found to be terminal. HGSOC represents 70% of all subtypes of ovarian cancers.

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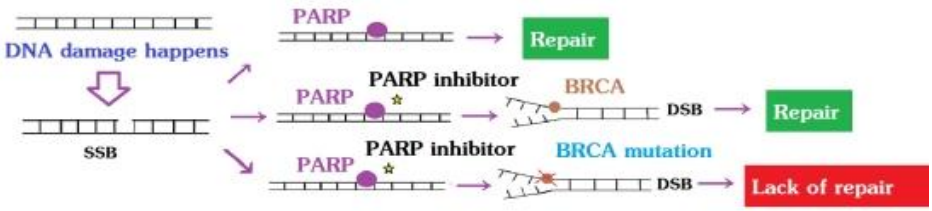


Figure 1. DNA damage and repair processes involved in PARP and BRCA: DNA damage happens and SSBs produced. PARP can recognize SSBs and repair DAN damage. Impact of PARP can be prevented by PARP inhibitors, resulting the generation of DSB. BRCA are significant in repairing DSBs. All in all, either PARP or BRCA works properly to repair DNA damage. However, Both PARP and BRCA failed to work, resulting DNA damage repair cannot be completed.

The Cancer Genome Atlas (TCGA) project analyzed the express of RNA and mRNA, promoter methylation, DNA copy number, and DNA sequences encoding gene exons [7]. In 316 samples, 303 samples mutated TP53 ,approximately 96% [8]. For this reason, we can conclude that HGSOC is characterized by TP53 mutations. TP53 is a tumor suppressor gene that encodes a protein P53, preforms most of its role by playing the part of a sequence-specific DNA-binding transcription factors that dominates the cell cycle onset, plays a vital role in DNA repair, the regulation of proliferating cell, genomic stability, metabolic homeostasis apoptosis, senescence, and apoptosis [9]. Kuhn E et al. simultaneously performed 29 pelvic (non-uterine) HGSOCs of STICs, extracted DNA after microdissecting cells with a 30-gauge needle under a microscope, performed PCR amplification, and carried out TP53 mutation analysis. As result, of 29 examined case, 17 missense mutation(~59%), 9 frameshift mutation, 3 splice mutation, 1 nonsense mutation(Table 1) [9].

Besides, 13% samples happened BRCA1 or BRCA2 mutations, part of them are ascribed to familial HGS0C, and another part BRCA1 or BRCA2 mutation are incativated via other machanism, such as hypermethylation of the BRCA1 promoter [10]. BRCA1/2 genes have correlations of hereditary breast cancer, play important effect in inhibiting taking place of vicious cancer and governing the replication of human cells, DNA damage and repair and normal growth of cell. BRCA1 /2 molecules encoded by BRCA1/2 genes are two significant components of the DNA homology-directed repair (HDR) that is required to repair DSBs. Once the BRCA molecules are deficient, the DSBs will not be repaired and then lead to cell death. DSBs inform when SSBs are not repaired. Once PARP is inhibited, the situations mentioned above will appears. (Figure 1)

The molecular genetic data derived mainly from studies of serous carcinoma indicates that BRAF, PTEN, KRAS oncogenes genetic alterations were found in low-grade serous ovarian carcinoma(LGSOC), at the same time TP53 are not find in LGSOC [10]. Result of whole-transcriptome sequencing (RNA sequencing) of 18 ovarian clear-cell carcinomas indicates somatic mutations in ARID1A (the AT-rich interactive domain 1A [SWI-like] gene) [11]. Through PCR amplification and Sanger sequencing, PIK3CA, KRAS, PPP2R1A, and ARID1A mutations were identified [12]. Anyway the type I tumors can be described as relatively genetically stable, and usually display all kinds of sequence mutations occurs in somatic cells, including BRAF, PTEN, KRAS, CTNNB1 (the gene encoding betacatenin), PIK3CA, ARID1A and PPP2R1A. However very rarely show TP53 mutation [5]. In the midst of somatic sequence mutations of type Ⅰ, BRAF and KRAS are the most important. A serine/threonine protein kinase of RAF/mil family encoded by BRAF gene,which is instrumental in cell division, differentiation and secretion, involving the regulation of MAP/ERKS signaling pathway. KRAS involved in signal transduction within the cell, When KRAS gene mutation, the gene permanently activated, failing produce normal RAS protein, so that cell signaling disorders, cell proliferation and cancer.

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Table 1. P53 alteration in serous tubal intraepithelial carcinoma and high-grade serous carcinoma: IHC = immunohistochemistry (% of tumour cells with intense nuclear staining), and a p53 monoclonal mouse antibody was used to perform IHC. All case with p53 positive control (overexpression) and negative control are conduct IHC. ≥ 60% of nuclei were positive, meaning correlation of TP53 missens mutation. By reading the table, 17 cases (case1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18) display missens mutation can be summarized [9].

	STIC-1		STIC-2		HGSC		
Case	**TP53 mutation**	**IHC**	**TP53 mutation**	**IHC**	**TP53 mutation**	**IHC**	**Mutation type**
1	E7 : 13380G>GA:248R>R/Q	100	E7 : 13380G>GA:248R>R/Q	100	E7 : 13380G>GA:248R>R/Q	60	Missense
2	E5 : 12457G>GT:157V>V/F	100	E5 : 12457G>GT:157V>V/F	100	E5 : 12457G>GT:157V>V/F	80	Missense
3	E8 : 13813C>CG:278P>P/R	100	NP	NP	E8 : 13813C>CG:278P>P/R	100	Missense
4	E7 : 13338A>AG,234Y>Y/C	100	E7 : 13338A>AG,234Y>Y/C	100	E7 : 13338A>AG,234Y>Y/C	100	Missense
5	E5 : 12478A>AG,164K>K/E	100	E5 : 12478A>AG,164K>K/E	100	E5 : 12478A>AG,164K>K/E	100	Missense
6	E4 : 11557T>TG,109F>F/C	100	E4 : 11557T>TG,109F>F/C	100	E4 : 11557T>TG,109F>F/C	100	Missense
7	E7 : 13349T>TC:238C>C/R	100	E7 : 13349T>TC:238C>C/R	100	E7 : 13349T>TC:238C>C/R	100	Missense
8	E8 :13772het_delA	100	NP	NP	E8 : 13772het_delA	100	Frameshift
9	E5 : 12512G>GA:175R>R/H	100	E5 : 12512G>GA:175R>R/H	100	E5 : 12512G>GA:175R>R/H	100	Missense
10	E7 : 13352A>AG:239N>N/D	100	NP	NP	E7 : 13352A>AG:239N>N/D	100	Missense
11	E7 : 13338A>AG:234Y>Y/C	100	E7 : 13338A>AG:234Y>Y/C	100	E7 : 13338A>AG:234Y>Y/C	100	Missense
12	WT (E5)	100	E5 : 12365A>AG:126Y>Y/C	100	E5 : 12365A>AG:126Y>Y/C	100	Missense
13	E5 : 12505G>GT:173V>V/L	100	E5 : 12505G>GT:173V>V/L	100	E5 : 12505G>GT:173V>V/L	100	Missense

Table 1. (continued).

14	E7 :	9	E7 :	95	E7 :	80	Missense

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	13350G>GA,238C>C/Y	5	13350G>GA,238C>C/Y		13350G>GA,238C>C/Y		
15	E5 : 12458T>TG,157V>V/G	70	E5 : 12458T>TG,157V>V/G	70	E5 : 12458T>TG,157V>V/G	90	Missense
16	E5 : 12515G>AG:176C>Y/C	60	E5 : 12515G>AG:176C>Y/C	90	E5 : 12515G>AG:176C>Y/C	75	Missense
17*	E8 : 13772het_delA	60	E8 : 13772het_delA	100	E8 : 13822A>T,281D>V	80	Missense
					E8 : 13772het_delA		Frameshift
18	E8 : 13772hom_delA	0	E8 :13772hom_delA	0	E8 : 13772hom_delA	0	Frameshift
19	E7 : 13363hom_delC	0	E7 : 13363hom_delC	0	E7 : 13363hom_delC	0	Frameshift
20	E5 : 12418C>CT:144Q>Q/X	0	NP	NP	E5 : 12418C>CT:144Q>Q/X	0	Nonsense
21	I6 : 12742G>GT	0	NP	NP	I6 : 12742G>GT	0	Splice
22	WT	0	NP	NP	I6 : 13308A>AT	0	Splice
23	E7 : 13363het_delC	0	E7 : 13363het_delC	0	E7 : 13363het_delC	0	Frameshift
24	I4 : 11607G>GA	0	WT	0	I4 : 11607G>GA (3′ intron 1)	0	Splice
25	E5 : 12379_12380het_insTC	0	NP	NP	E5 : 12379_12380het_insTC	0	Frameshift
26	E7 : 13328_13329ins†	0	NP	NP	E7 : 13328_13329ins†	0	Frameshift
27	WT	0	NP	NP	E6 : 12661G>GT:198E>E/X	0	Nonsense
28	E7 : 13402_13403insA	0	NP	NP	E7 : 13402_13403insA	0	Frameshift
29‡	E7 : 13315het_delC	0	E7 : 13315het_delC	0	E6 : 12638C>CT:190P>P/L	100	Missense
					E7 : 13315het_delC		Frameshift

3. Corroboration of targets

In 2005, Monk BJ et al discover bevacizumab (rhuMAB VEGF) is active in a case of recurrent, refractory serous carcinoma in the late stage, after documenting an objective and lasting response that lasted at least 5 months. During 5 months, every 3 week bevacizumab 15 mg/m2 is given intravenously after the failure of the eleventh line cytotoxic chemotherapy and radiation chemotherapy [13]. In the results of a clinical trial launched by Bradley J et al , A response rate of 16% was observed (all patients who received BEV treatment alone), of which 62.5% showed stable disease [14], which confirmed the validity of bevacizumab in therapy of EOC. Bevacizumab, a growth factor of humanized anti-vascular endothelial (VEGF) monoclonal antibody, exerts a therapeutic effect through combining VEGF. Under this situation, VEGF failure to combine surface receptors of endothelial

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cell, such as Flt-1 and KDR, thus affects endothelial cell proliferation and angiogenesis. Neoplasm angiogenesis and VM are crucial for serving neoplasm blood, tumour growth and metastasis [12]. For these reason, angiogenesis can be the targets of the therapy of ovarian cancer. Angiogenic factors VEGF, FGF, PDGF, and VEGF/VEGFR signal pathway are attached great importance in tumor angiogenesis. Due to problems of angiogenesis occur in the vast majority of cancers, lack of specificity, are not regarded as the focus of this article.

Combine several studies about relationship with HGSOC , STIC, and TP53, the important of TP53 can be deduced [9]. Therefore, TP53 can be regarded as a potential targets, used to treat type Ⅱ of ovarian cancer, especially HGSOC. There has been a lot of research on TP53. Research indicates that MDM2 and MDM4 works as regulators of TP53, directly plays a negative regulating role. MDM2 and MDM4 downregulate transcriptional activity of TP53. MDM2 target TP63 to the ubiquitin–proteasome protein degradation pathway . For this reason, MDM2/MDM4 can be regarded as another target for ovarian cancer treatment. Several compounds have emerged to prevent MDM2/MDM4 binding with WT p53, thereby preventing its degradation. For example, nutlins, MDM2/4 antagonist, such as PRIMA-1MET. specific MDM2–p53 nutlin antagonists). Moreover, miRNA directly or indirectly affects the expression of TP53, positive or negative impact. Upregulation of miRNAs associated with negative effects or downward regulation of miRNAs associated with positive effects both impair the TP53 pathway [15]. That offer a new way for ovarian cancer treatment. However, because of TP53 mutation happens 50% of invasive tumors, including HGSOC, triple-negative breast cancers (TNBC), oesophageal cancers, small-cell lung cancers (SCLC) and squamous cell lung carcinoma (NSCLA), weak specificity. Meanwhile researches about TP53 have no major breakthrough. Therefore, Is not the focus of this article.

Due to BRCA-deficient ovarian cancer patients lack expression of BRCA1/2, PRAP is critical in repairing SSBs. The "synthetic lethal" theory makes it reasonable to apply PARP inhibitors to BRCA-deficient ovarian cancer patients [11]. Fracture repair of SSBs requires involvement of PARP1/2, and PARP1 is also required for repairing DSBs and injury of replication fork . In 2005, Farmer H et al and Bryant HE et al separately discovered and confirmed unexpectedly and profoundly ,BRCA1/2 dysfunction sensitizes cells to the inhibition of PARP enzyme activity [16, 17]. After phase I clinical trial, Recommended dose was commend. Result of phase II clinical trial conduct by Gelmon KA et al indicates confirmed objective responses were seen in 7 of 17 patients with BRCA1 or BRCA2 mutations [18]. Lots of SOLO-1/SOLO-2 studies have confirmed the results proposed. Moreover, Because PARP inhibitor own pertinence in the treatment of EOC, and great breakthrough has been made in the research. PARP inhibitor is an ideal research direction. Currently available PARP inhibitors include olaparib, talazoparib, veliparib, niraparib, rucaparib. Among them, olaparib is focus of the following discussion.

4. Inspiration

In 1994, a man submitted an application to the World Cancer Research Corporation for a grant for a project to find a new cancer drug, which was certified by professional scientists, and the application was approved. His name was Steve. He began studying how proteins in human cells repair DNA damage. He knew that DNA is fragile and can be easily damaged. The repair process was critical to maintaining the health of the body's cells. The World Cancer Research Center funded three more of his projects. Finally, in 1997, Steve discovered that defects in DNA repair could be exploited. But even though he made great progress, there were still no pharmaceutical companies to support his discovery. Finally, steve founded his own company called KuDOS to do his own production and research.

KuDOS laid the groundwork for the development of many drugs. After several years of development and testing, Steve and his team finally developed a drug called Olaparib. Because KuDOS did not have the money to conduct clinical biological testing of this drug, Steve decided to sell Olaparib and KuDOS to another international pharmaceutical company, AstraZeneca, to ensure that Olaparib had excellent future prospects. Eight years later, using Olaparib to treat patients, who have certain types of advanced ovarian cacer, got approvals in the United States and the European

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Union. The drug has other promising developments: Olaparib has also performed well in the treatment of certain types of pancreatic cancer, prostate cancer and breast cancer. In the United States, olaparib is already approved for the treatment of these cancers. While Steve and the research team were conducting this study, Steve's grandmother was confirmed to have advanced ovarian cancer and could no longer use normal chemotherapy. Finally, she tried Steve's latest drug and was cured successfully.

5. History

In December 2014, the EMA and the FDA cleared olaparib [2, 19].

January 2018, olaparib was certified by the FDA as the first PARP inhibitor that gBRCAm metastatic breast cancer could be treated.

August 2017, Olaparib tablets were reported to be allowed to treat adult patients with recurrent EOC, FTO, o rPPC in the United States, as patients who were used in clinical trials all responded well to this pill [20, 21].

January 2018, olaparib got approval of FDA in the United States to treat certain types of breast cancer that have spread because the tumor has a specific genetic mutation. the first drug of the PARP inhibitor type got approval in treating breast cancer, this is also the first drug approved for the therapy of metastatic breast cancer with certain "BRCA" gene mutations

December 2018, using olaparib for miantenance therapy of fallopian tube cancer (FTC), primary peritoneal cancer (PPC), advanced epithelial ovarian cancer (EOC) got approval.

December 2019, olaparib got approved for maintenance therapy of metastatic pancreatic cancer with a deleterious or suspected deleterious germline BRCA mutation (gBRCAm)

In March 2022, olaparib is approved for the adjuvant treatment of adults with negative high-risk early-stage breast cancer.

6. Mechanism

Olaparib reduces the efficiency of polymerase (ADP-ribose) and the repair of single strands of DNA by blocking the production of polymerase. Because cancer cells have the ability to reorganize cells, olaparib causes BRCA-associated cancer cells to die as a result.

7. PRAP

In the course of each cell cycle, DNA damage happens in thousands of times so cell repair and regeneration is necessary, including in cancer cells. Otherwise, when cells are damaged they die if there is no subsequent activity. The principle of chemotherapy and radiotherapy is to increase the damage of cancer cells in the cell cycle to the extent that they fail to be successfully repaired, resulting in cancer cells death.

BRCA1/2 and PARP2 are important for repair of DNA breaks. When the gene for one of these proteins is mutated, the self-repair of DNA can go awry. When this damage is severe enough, the altered gene can lead to cell death.

PARP1 is a vital protein that works in repairing single-strand breaks. If this gap must remain unrepaired until the cell divides, then replication itself causes double strand to breaks, which as well as called DSB.

Drugs that inhibit PARP1 make DSB in this way. In tumors performing BRCA1/2 and PARP2 mutations, DSB lack of repair, resulting in cell death.

PARP inhibitors not only block the catalytic action of PARP proteins, but also cause PARP proteins to be restricted to DNA. This prevents replication and can lead to cancer cell death more efficiently, due to the fact that cancer cells grow much faster than relative to other cells.

Cancer cells that form in a short period of time are sensitive to PARP inhibitors.

8. Conclusion

Started with discussing pathogenesis of ovarian cancer, genes mutation of different subtypes ovarian cancers is confirmed. In accordance with pathogenesis, target studies were gradually launched, finding

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angiogenesis, TP53, and PARP can be the target therapy studies. PARP inhibitor olaparib are chose to discuss in this article for PARP own pertinence compare with angiogenesis and TP53. By research PARP inhibitor, discovering process and treatment mechanism of olaparib are showed in this assay. As PARP inhibitor, olaparib works through preventing repairing DNA damage in gBRCA mutation ovarian cancer. Since the discovery and development process of Olaparib set a rather considerable example for rational drug design, such bottom-up scheme starting from target discovery should be attached with great priority. Given the progression of advanced techniques, successful drug design cases with rational understanding in atomic level have been witnessed more often. It is more confidence to believe that those human disease problems preventing us from healthy long lives would be finally solved by pharmaceutical researchers soon.

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