**Insulin-like Growth Factor-I Receptor Signaling Blockade Combined with Radiation**

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**Abstract**

Signaling through the insulin-like growth factor-I receptor (IGF-IR) is implicated in cellular proliferation, apoptosis, carcinogenesis, metastasis, and resistance to cytotoxic cancer therapies. Targeted disruption of IGF-IR signaling combined with cytotoxic therapy may therefore yield improved anticancer efficacy over conventional treatments alone. In this study, a fully human anti-IGF-IR monoclonal antibody A12 (ImClone Systems Inc, New York, NY) is examined as an adjunct to radiation therapy. IGF-IR expression is shown for a diverse cohort of cell lines, whereas targeted IGF-IR blockade by A12 inhibits IGF-IR phosphorylation and activation of the downstream effectors Akt and mitogen-activated protein kinase. Anchorage-dependent proliferation and xenograft growth is inhibited by A12 in a dose-dependent manner, particularly for non–small cell lung cancer lines. Clonogenic radiation survival of H226 and H460 cells grown under anchorage-dependent conditions is impaired by A12, demonstrating a radiation dose-enhancing effect for IGF-IR blockade. Post-radiation anchorage-independent colony formation is inhibited by A12 in A549 and H460 cells. In the H460 xenograft model, combining A12 and radiation significantly enhances antitumor efficacy compared with either modality alone. These effects may be mediated by promotion of radiation-induced, double-stranded DNA damage and apoptosis as observed in cell culture. In summary, these results validate IGF-IR signal transduction blockade as a promising strategy to improve radiation therapy efficacy in human tumors, forming a basis for future clinical trials. [Cancer Res 2007;67(3):1155–62]

**Introduction**

A protein of significant interest in cancer therapeutics is the insulin-like growth factor receptor-I (IGF-IR), a membrane-bound tyrosine kinase receptor that plays a role in tumor cell proliferation, differentiation, apoptosis, and metastasis (1, 2). Overexpression of IGF-IR or the soluble ligands IGF-I and IGF-II is shown in a broad spectrum of malignancies arising from breast (3, 4), prostate (5, 6), colon (7), lung (8), melanoma (9), ovary (10), and myeloid origin (11). Epidemiologic studies also reveal a link between elevated serum IGF-I and IGF-II levels and an increased incidence of breast, prostate, and colon cancer (12). Furthermore, IGF-IR signaling is known to mediate resistance to cytotoxic chemotherapy and radiation, raising the possibility that targeted disruption of the IGF-IR axis may afford a therapeutic advantage when combined with either of these conventional cancer treatments (13–15).

The development of clinically useful methods to inhibit IGF-IR signaling has been hindered by cross-reactivity with the insulin receptor. Methods including mouse monoclonal antibodies, antisense strategies, receptor inhibitor peptides, and dominant-negative constructs show antiproliferative efficacy in preclinical model systems but are not easily translated into clinical use (16–20). Recently, IGF-IR–specific, small-molecule tyrosine kinase inhibitors and humanized or fully human monoclonal IGF-IR antibodies have been developed, enabling preclinical testing with the potential for clinical use (21–26). The fully human monoclonal antibody A12 (ImClone Systems Inc., New York, NY) was developed by screening a human Fab phage display library to yield a high-affinity monoclonal antibody (4.11 × 10^−11 mol/L, IC_{50} 0.6–1 nmol/L) that inhibits IGF-IR activation and signaling through the downstream effector mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3’-kinase/Akt pathways without significant insulin receptor cross-reactivity (21). Preclinical testing of A12 in human cancer cells results in apoptosis induction by two distinct mechanisms: first, by blocking the interaction of IGF-IR and its ligands and, second, by mediating IGF-IR internalization and degradation (21).

Promotion of apoptosis is one mechanism by which inhibition of growth factor signaling may enhance the therapeutic efficacy of radiation, as suggested by preclinical studies of the epidermal growth factor receptor (EGFR; refs. 27, 28). Combining EGFR inhibition with radiation has recently shown potent survival benefit in a phase III clinical trial (29). Given the involvement of IGF-IR in diverse oncologic processes, including apoptosis, we hypothesized that targeted IGF-IR signaling inhibition might similarly enhance the efficacy of radiation in tumors where IGF-IR activation is a component of the cancer phenotype. We therefore did studies to identify cell lines in which IGF-IR signaling inhibition results in proliferation inhibition. The interaction between A12 and radiation was subsequently characterized in these lines, demonstrating enhancement of radiation-induced apoptosis, clonogenic survival, and xenograft growth inhibition for tumor cells exposed to A12 and radiation. These results suggest that interruption of IGF-IR signaling may be a therapeutically useful adjunct to radiation therapy.

**Materials and Methods**

**Reagents.** Cell culture media were obtained from Life Technologies, Inc. (Gaithersburg, MD). SeaPlaque low-melting temperature agarose was purchased from Cambrex BioScience (Rockland, ME). Propidium iodide,
Apoptosis assays. To assess the activation of effector caspases, a sulforhodamine-labeled fluoromethyl ketone peptide inhibitor of caspase (SR-VAD-FMK) assay was done using the Caspase assay (Chemicon, Temecula, CA). Attached and floating cells were then harvested and exposed to SR-VAD-FMK at 37°C for 1 h. After washing out membrane-bound fluorophore, aliquots were assayed on a fluorescence plate reader at 550 nm/595 nm (excitation/emission). The downstream apoptosis effector molecule Bax was assayed by immunohotting of total cellular lysates. Cells were grown either in the presence or absence of A12 for 24 h with 1% serum. Cells in the experimental groups were irradiated (8 Gy) and cultured for 48 h before protein harvest.

Clonogenic radiation survival assay. Survival after radiation exposure was defined as the ability of the cells to maintain their clonogenic capacity by forming colonies after radiation exposure. Cells were exposed to either A12 or human IgG for 48 to 72 h and subsequently irradiated at 0 to 5 Gy with a Shepherd & Associates Model 109 irradiator (San Fernando, CA) and a cesium-137 source. Cells were then trypsinized, counted, and seeded for colony formation in six-well plates at 50 to 5,000 per well. Cells were incubated from 7 to 21 days with medium changes every 48 to 72 h. At the end of the experiment, colonies were stained with crystal violet and manually counted. Colonies consisting of 50 or more cells were scored, and 4 to 10 replicate wells containing 10 to 150 colonies per well were counted for each condition.

Soft agar colony formation assay. Soft agar colony-forming assays were done with modifications to a previously described protocol (30). Agarose (0.5%) was prepared in complete RPMI medium and allowed to solidify as the bottom layer in 24- or 6-well plates. Exponentially growing cells were harvested and incubated in 100 µL PBS containing various A12 or human IgG concentrations for 15 min before embedding in a 0.35% top agarose layer with complete RPMI medium and three to five replicates per condition. Plates were incubated for 15 to 30 min at room temperature to allow the top layer to solidify. To allow cells to recover, plates were incubated for 12 h at 37°C before irradiation and subsequently returned to the incubator for 7 to 14 days. At the conclusion of the experiment, colonies were visualized after exposure to MTX for 2 to 2 h at 37°C. Plates were digitized with a computer-based scanner and colonies were manually counted for quantification.

Detection of double-stranded DNA damage. Cells were seeded at 3,000 per well on four-well culture coated slides (Nalgé Nunc Int., Rochester, NY) and allowed to attach overnight. Cells were subsequently exposed to A12 (100 µmol/L) or IgF-1 (50 µg/mL) in 1% serum for 48 h followed by 6 Gy irradiation. Cells were fixed in methanol/3% acetic acid at 6 and 24 h postirradiation followed by processing for pH2AX immunocytochemistry and DAPI nuclear staining. Nonspecific antigen sites were blocked for 30 min in 3% bovine serum albumin. Anti-phospho-histone H2AX antibody (1:450) was applied for 1 h at room temperature. After washing, AlexaFlour488–conjugated anti-mouse antibody was used to label the primary antibody, and DAPI staining was done. Cells were mounted in ProLong Antifade medium and visualized with a ×40 objective using an Olympus BX51 fluorescent microscope (Olympus America, Inc., Melville, NY) and photographed with a SPOT RT color charged coupled device camera (Diagnostic Instruments, Inc., Sterling Heights, MI).

Xenograft growth in athymic nude mice. Athymic nude mice (3- to 4-week-old females) were obtained from Harlan Bioproducts for Science (Indianapolis, IN) and maintained in a laminar airflow cabinet under aseptic conditions. The care and treatment of experimental animals was in accordance with institutional guidelines. Approximately 1 × 10^6 cells were injected s.c. into the flank area (two tumors per animal) on day 0. Tumor volume was determined by direct measurement with calipers and calculated by the formula π/6 × (large diameter) × (small diameter)^3. Animal experiments generally included four treatment groups: control, radiation alone, A12 alone, and radiation in combination with A12. A12 was administered by i.p. injection at the specified doses and intervals. Radiation treatment was delivered via precision photon beam from a Varian (Palo Alto, CA) orthovoltage machine using custom-designed mouse jigs that immobilized the animals and specifically exposed the dorsal flank...
(harboring tumor xenografts) for irradiation without exposing non-tumor-bearing normal tissues.

**Immunohistochemistry.** IGF-IRβ, PCNA, and α-tubulin expressions were detected in xenograft histologic sections using immunohistochemistry. At xenograft harvest, animals were euthanized and tumor specimens were excised and fixed in 10% neutral-buffered formalin. After embedding in paraffin, 5-μm tissue sections were cut and mounted. Sections were dried, deparaffinized, and rehydrated. After quenching endogenous peroxidase activity and blocking nonspecific binding sites, slides were incubated at 4°C overnight with a 1:100 primary antibody dilution followed by a 30-min incubation of biotinylated goat anti-mouse secondary antibody. Tissue sections were then incubated with streptavidin peroxidase and visualized with the 3,3′-diaminobenzidine chromogen (Lab Vision Corporation, Fremont, CA).

**Statistical analysis.** The effect of A12 on cellular proliferation inhibition, xenograft growth inhibition, clonogenic survival, and caspase activation was assessed by unpaired two-tailed Student’s *t* test with GraphPad Instat software (GraphPad Software, San Diego, CA). For comparisons between more than two treatments in the xenograft experiments, multiple regression analysis was done. If not otherwise indicated, error bars in all experiments represent the SD.

**Results**

**IGF-IR expression and signal transduction.** To establish the IGF-IR expression profile across a selection of diverse cancer cell lines, immunoblotting was done on total protein derived from human breast (MCF-7, SKBr3), prostate (DU145, PC3, LNCaP), lung (H226, A549), head and neck (SCC1, SCC6), brain (T98G), and vulvar (A431) cell lines (Fig. 1A). IGF-IR protein expression was shown in all cell lines tested, including expression in the non-small cell lung adenocarcinoma H460, colon adenocarcinoma HT29, and pancreatic line BxPC3 (data not shown). EGFR levels were simultaneously assessed, demonstrating greater variability of expression across cell lines and no measurable protein expression in MCF-7 and LNCaP cells. Thereafter, we evaluated the efficacy of IGF-I signaling blockade by A12 in the H460 and A549 cell lines. Robust induction of IGF-IR phosphorylation and phosphorylation of the downstream effector proteins MAPK and Akt was seen after 30-min exposure to IGF-I when compared with serum-starved or A12-treated controls (Fig. 1B). IGF-I–dependent phosphorylation of IGF-IR and MAPK was abrogated by 30-min pretreatment with A12, and Akt phosphorylation was reduced, demonstrating the ability of A12 to inhibit IGF-I–dependent signaling through IGF-IR.

**Effect of IGF-IR blockade on cell proliferation.** An array of human cancer cell lines was treated with A12 to assess the antiproliferative effect of IGF-IR blockade under anchorage-dependent conditions (Fig. 2A). As a proxy for cellular viability and proliferation status, MTT assays were used to determine the activity of cellular mitochondrial dehydrogenase. For T98G and A549 cells, antiproliferative effects were essentially undetectable, regardless of A12 dose level. More pronounced dose-dependent antiproliferative effects were seen for MCF7, H460, PC3, SCC1483, and HT29 cells, whereas more modest antiproliferative activity was noted for DU145, SCC1, SCC22B, A431, H226, SCC6, and BxPC3 lines. No correlation between IGF-IR protein levels and antiproliferative activity was noted; however, cell lines known to secrete IGF-I in an autocrine loop (MCF-7, HT29, and H226) were among the most sensitive to IGF-IR signaling inhibition (31–33). When A12 antiproliferative effects were observed, dose-dependent proliferation inhibition was seen between 1 and 1,000 nmol/L, indicating that no dose plateau was reached at the highest dose level. Quantitatively greater antiproliferative effects were seen for A549, H460, and MCF7 cells cultured under anchorage-independent conditions, consistent with previous reports (data not shown; refs. 17, 30, 34).

**A12 activity in tumor xenografts.** To determine the effect of A12 on tumor cell proliferation in vivo, H226 xenografts were established in athymic mice. A12 or isotype-matched IgG (1 mg) was delivered i.p. twice weekly beginning on day 15 after tumor cell inoculation, when tumors exceeded 50 mm³ (*n* = 4 tumors per group). By the 3rd week of treatment, there was a 3.2-fold reduction in tumor volume in the A12-treated animals versus IgG controls (*P* < 0.0001; Fig. 2B–C). Xenograft specimens were subsequently analyzed by immunohistochemistry. IGF-IR expression in A12-treated tumors was qualitatively decreased compared with controls. Moreover, expression of the tumor cell proliferation marker PCNA was qualitatively lower in A12-treated tumors relative to controls. These results suggest that in addition to IGF-IR signal blockade, A12 impairs H226 cell proliferation in vivo by down-regulation of IGF-IR.

**Clonogenic radiation survival.** Growth factor signaling blockade combined with radiation results in favorable anticancer activity across several growth factor families and cell lines. To determine whether IGF-IR signal blockade results in a similar effect, clonogenic radiation survival assays were done using the H460 and H226 cell lines grown under anchorage-dependent conditions with A12 pretreatment and three single-fraction radiation dose levels. Reduced clonogenic survival was observed in H460 cells (Fig. 3A) and H226 cells (Fig. 3B), with a modest radiation dose-enhancement factor of 1.2 for both cell lines. These results show a favorable interaction between IGF-IR blockade and radiation in H460 and H226 cells.
Anchorage-independent colony formation. As qualitatively greater antiproliferative activity was observed with IGF-IR blockade in cells grown under anchorage-independent conditions, colony-formation assays combining A12 and radiation were done with the A549 and H460 cell lines. Cells were cultured in the absence or presence of A12 and irradiated at three dose levels with subsequent assessment of colony formation. Qualitatively fewer and smaller colonies were consistently observed in cells exposed to the combination of A12 and radiation compared with radiation alone (Fig. 3C). Quantitatively, 20% to 30% fewer colonies were noted for cells exposed to both A12 and radiation compared with radiation alone, regardless of radiation dose level (Fig. 3D–E). These results suggest that IGF-IR blockade interacts with radiation to inhibit A549 and H460 anchorage-independent colony formation and...
growth. Although showing a similar trend as seen in the clonogenic radiation survival experiments, colony-formation curves from the soft agar assays cannot be compared directly to the clonogenic survival assays, because irradiation was done after cell recovery in the soft agar medium. In the clonogenic survival assays, irradiation was done before single-cell plating. Even with these differences in technique, the results are complementary and indicate an interaction between A12 and radiation in cells grown under anchorage-dependent and anchorage-independent conditions.

Radiation-induced apoptosis. One mechanism by which growth factor blockade may result in increased radiation efficacy is through promotion of apoptotic cell death (35). We therefore did caspase activation assays in H226 cells combining IGF-IR blockade and radiation. A 3.1- and 3.9-fold induction of caspase activity relative to radiation (8 Gy) or A12 (100 nmol/L), respectively, was observed for H226 cells exposed to both treatments (Fig. 4A). Furthermore, both A12 and radiation alone or in combination induced the proapoptotic effector protein Bax in H226 and H460 cells as measured by immunoblotting (Fig. 4B). These results indicate that A12-mediated IGF-IR signaling blockade combined with radiation promotes caspase-mediated apoptosis in H226 and H460 cells.

Radiation-induced, double-stranded DNA damage. The efficacy of radiation-induced cell lethality is augmented by inhibition of DNA double-stranded break repair. IGF-1 signaling may counteract UV- or radiation-induced DNA damage by
promoting DNA repair (36–38). We therefore characterized the effect of IGF-I and A12 on the formation and repair of radiation-induced DNA double-stranded breaks by detecting phospho-histone H2AX complexes (γH2AX) in irradiated H460 cells. γH2AX H2AX is a sensitive indicator of radiation-induced DNA double-stranded breaks and is readily detected by immunocytochemistry (39, 40). Induction of γH2AX foci was observed at 6 h after 6 Gy irradiation in untreated control cells and in cells exposed to A12 (Fig. 5A). Qualitatively, pretreatment with IGF-I inhibited the formation of γH2AX complexes; however, simultaneous A12 treatment abrogated this effect (Fig. 5A). At 24 h after irradiation, expression of γH2AX foci in control and IGF-I–treated cells was minimal; however, persistent γH2AX complexes were observed in cells treated with A12 either in the absence or presence of IGF-I (Fig. 5B). These results suggest that IGF-I promotes repair of radiation-induced DNA double-stranded breaks, a process that is inhibited by A12. Furthermore, A12 promotes formation of persistent DNA double-stranded breaks at 24 h postirradiation either in the presence of absence of IGF-I.

A12 and radiation in tumor xenografts. Having established a positive interaction between IGF-IR blockade and radiation in vitro, we did a parallel study in mice bearing tumor xenografts. H460 tumor cells inoculated into the flanks of athymic mice were grown to ~ 80 mm³. After loading with 2.5 mg isotype-matched IgG or A12 on day 15, i.p. IgG or A12 (1 mg) injections were delivered twice weekly. Animals within each group were stratified by tumor size and assigned to either no additional treatment or focal radiation directed to the tumor at 1.5 Gy per fraction, once weekly for 4 weeks. In total, tumor volumes were obtained and compared for four groups: IgG alone, A12 alone, IgG and radiation, and A12 and radiation (Fig. 6). By the 2nd week of treatment, statistically significant differences in tumor volume were noted between all groups. An incremental reduction in tumor volume compared with IgG controls was noted for all groups receiving treatment: A12, radiation, or A12 combined with radiation. At the conclusion of treatment, animals receiving both A12 and radiation harbored tumors 3.1-fold smaller than IgG controls (P < 0.001). Tumors from animals receiving either A12 or radiation alone were 1.3-fold (P < 0.05) and 1.8-fold (P < 0.001) smaller than controls, respectively. These results indicate antitumor activity for both A12 and radiation in H460 xenografts and additive antitumor effects for combined A12 and radiation.

Discussion

Although mouse monoclonal antibodies against IGF-IR have been available for several decades, anti–IGF-IR agents suitable for testing in humans have only recently become available. A major obstacle to selective IGF-IR targeting is the high degree of homology between IGF-IR and the insulin receptor, making receptor-specific inhibition challenging. Recent advances in human monoclonal antibody engineering and small-molecule tyrosine kinase inhibitor screening has yielded several fully human or humanized anti–IGF-IR monoclonal antibodies and IGF-IR–specific tyrosine kinase inhibitors (21–26, 34). Although these compounds remain early in their development, preclinical data justifying their investigation in cancer therapy is emerging. As with other target-specific therapies, the particular promise for IGF-IR inhibition may lie in combination with cytotoxic radiation or chemotherapy, a strategy further justified by the role of IGF-IR in resistance to these modalities (13–15).
In the present study, we examined the interaction between A12-induced IGF-IR blockade and radiation. Human tumor cell lines demonstrating impaired anchorage-dependent and anchorage-independent proliferation in the presence of A12 were used in clonogenic survival assays, anchorage-independent colony formation assays, and in xenograft studies. We found that the H226 and H460 cell lines grown under anchorage-dependent conditions exhibited impaired radiation survival in the presence of A12 when compared with controls (Fig. 3). Postradiation anchorage-independent colony formation of H460 and A549 cells in soft agar was similarly inhibited by A12 treatment (Fig. 3C-E). Extending these findings to an in vivo model, H460 xenograft growth was substantially inhibited with systemic A12 administration combined with radiation compared with either treatment alone (Fig. 6). Promotion of radiation-induced apoptosis (Fig. 4) and inhibition of IGF-1–mediated DNA double-stranded break repair (Fig. 5) are two mechanisms by which A12 may interact favorably with radiation.

Several lines of experimental evidence validate IGF-IR signaling blockade as an important anticancer target that may prove clinically useful in conjunction with radiation therapy. In a mouse embryo model system, an IGF-1–mediated cytoprotective effect was observed (41) and subsequently shown to exert entereic radioprotection in an animal model, thought to be a consequence of antiapoptotic effects (42). IGF-IR overexpression is also known to mediate radiosensitivity. As evidence of this, fibroblasts expressing high IGF-IR levels are relatively radiosensitive compared with controls (13). In this same study, tumor samples from patients undergoing surgery and radiation for breast cancer were analyzed by immunohistochemistry for IGF-IR expression. High tumor levels of IGF-IR correlated with ipsilateral breast tumor recurrence during the first 4 years after treatment but no correlation was observed for late relapses, suggesting an IGF-IR–mediated radiation resistance. Protection from radiation-induced apoptosis is a potential mechanism by which IGF-IR may mediate these effects, a function possibly arising from tyrosine phosphorylation sites within the COOH-terminal domain that promote signaling through the MAPK pathway (15). Another mechanism by which IGF-IR may mediate radiosensitivity is through modulation of DNA damage repair, suggested by a study of irradiated mouse cells overexpressing IGF-IR, showing that DNA replication time was slowed in these cells relative to parental controls (43). Further evidence comes from ATM-deficient cells that are highly radiosensitive and also deficient in IGF-IR expression. IGF-IR overexpression in these cells subsequently normalized the radiation response (44). Down-regulation of ATM and impaired postradiation ATM kinase activation has also been observed in cells where IGF-IR expression is inhibited (45). IGF-1 is also known to enhance genomic stability by promoting homologous recombination-directed DNA repair of DNA double-stranded breaks caused by irradiation (36). Blockade of IGF-IR signaling may therefore delay or abrogate radiation-induced DNA double-stranded break repair, a hypothesis supported by the present study.

Increased IGF-IR expression has been observed in glioblastoma multiforme cell lines after irradiation, possibly contributing to the radioresistant phenotype in these cells by mechanisms described above (46). Indeed, several tumor types express high levels of IGF-IR in the absence of radiation induction, including breast, colon, lung, and prostate cancers (47). Blockade of IGF-IR signaling in these tumor types is therefore an attractive therapeutic strategy either alone or in combination with radiation or chemotherapy.

In addition to the current study, several lines of preclinical evidence support the concept that IGF-IR targeting may translate into clinical benefit when combined with radiation. IGF-IR–null mouse embryo fibroblasts exhibit increased sensitivity to radiation compared with wild-type cells (48). Mouse monoclonal antibodies have also been used to abrogate IGF-IR signaling in cell culture and xenograft tumor models in combination with cytotoxic therapy. Colon cancer cells treated in vitro with a combination of 5-fluorouracil and irradiation showed augmented cytotoxicity when treated with the anti–IGF-IR mouse monoclonal antibody 913 (49). Similar results were observed in mouse melanoma cells using antisense RNA (45). IGF-IR tyrosine kinase inhibition strategies yield similar radiosensitizing effects. Breast cancer cells treated with the tyrosine kinase inhibitor tyrophostin AG 1024 were more sensitive to radiation than untreated controls (50). Gene therapy approaches have also successfully targeted the IGF-IR. Adenoviruses expressing a dominant-negative truncated IGF-IR increased the sensitivity of pancreatic cancer cells and xenografts to radiation and chemotherapy-induced apoptosis (51). These results were extended to xenograft models of lung and colon cancer, with the observation that IGF-IR down-regulation also resulted in decreased activation of Akt (52). The potential for IGF-IR inhibition to enhance the cytotoxicity of radiation and chemotherapy in prostate cancer cells exhibiting both wild-type and mutant PTEN has been recently reported (53). In this study, IGF-IR silencing by small interfering RNA increased sensitivity to both chemotherapy and radiation in two prostate cancer cell lines, regardless of PTEN status.

Because of its defined role in establishing and maintaining the cancer phenotype, IGF-IR is a promising anticancer therapy target. Evidence suggesting a link between IGF-IR signaling and resistance to cytotoxic therapies provides rationale for combining IGF-IR inhibitors with radiation or chemotherapy, particularly for tumors that rely on IGF-IR signaling for growth and survival. The present study is the first published report to show a favorable interaction between radiation and IGF-IR blockade with an agent suitable for clinical translation, forming a rational basis for future investigative clinical trials.

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