Drug treatment


Integrated results from the COPERNICUS and GALILEO studies.


OBJECTIVES: To report on the efficacy and safety of intravitreal aflibercept in patients with macular edema secondary to central retinal vein occlusion (CRVO) in an integrated analysis of COPERNICUS and GALILEO.

PATIENTS AND METHODS: Patients were randomized to receive intravitreal aflibercept 2 mg every 4 weeks or sham injections until week 24. From week 24 to week 52, all intravitreal aflibercept-treated patients in both studies and sham-treated patients in COPERNICUS were eligible to receive intravitreal aflibercept based on prespecified criteria. In GALILEO, sham-treated patients continued to receive sham treatment through week 52.

RESULTS: At week 24, mean gain in best-corrected visual acuity and mean reduction in central retinal thickness were greater for intravitreal aflibercept-treated patients compared with sham, consistent with individual trial results. At week 52, after 6 months of intravitreal aflibercept as-needed treatment in COPERNICUS, patients originally randomized to sham group experienced visual and anatomic improvements but did not improve to the extent of those initially treated with intravitreal aflibercept, while the sham group in GALILEO did not improve over week 24 mean best-corrected visual acuity scores. Ocular serious adverse events occurred in <10% of patients.

CONCLUSION: This analysis of integrated data from COPERNICUS and GALILEO confirmed that intravitreal aflibercept is an effective treatment for macular edema following CRVO.

PMID: 28883712 PMCID: PMC5574701

SAVE-AMD: Safety of VEGF Inhibitors in Age-Related Macular Degeneration.


OBJECTIVE: To determine whether intraocular treatment with vascular endothelial growth factor (VEGF) inhibitors change systemic endothelial function (EF) in patients with neovascular age-related macular degeneration (AMD).

METHODS: In this prospective, randomized, 2-center, double-masked controlled interventional trial,
patients with neovascular and dry AMD were enrolled. Eligible neovascular AMD patients received 2 intravitreal loading doses of either ranibizumab 0.5 mg or bevacizumab 1.25 mg at 4-week intervals and were subsequently followed every 4 weeks and treated according to a pro re nata regime for up to 1 year. Patients with dry AMD served as controls. The primary endpoint was the change in EF assessed by flow-mediated dilatation (FMD) after 2 months of treatment with VEGF inhibitors in patients with AMD compared to patients with dry AMD. FMD was assessed with B-mode high-resolution ultrasonography of the left brachial artery.

RESULTS: 24 patients with neovascular AMD and 26 patients with dryADM were included in the trial. Treatment with VEGF inhibitors did not significantly change FMD (from 4.7 ± 2.4 to 3.9 ± 1.9% after 8 weeks, p = 0.07, and to 5.1 ± 2.0% after 1 year; p = 0.93 vs. baseline, respectively).

CONCLUSIONS: EF did not significantly differ between patients with neovascular AMD treated with intravitreal VEGF inhibition and patients with dry AMD.

PMID: 28866675

J Fr Ophtalmol. 2017 Aug 30. [Epub ahead of print]

[A "fast track" to improve management of neovascular age related macular degeneration]. [Article in French]


OBJECTIVE: To evaluate the role of a fast track for management of patients with neovascular age-related macular degeneration (nARMD) treated by intravitreal injection of anti-VEGF.

PATIENTS: The records of 100 patients in the chronic maintenance phase of intravitreal anti-VEGF followed in the fast track and 63 patients followed in the standard protocol for at least 12 months were retrospectively analyzed.

METHOD: Patients in the fast track underwent visual acuity (VA) testing by ETDRS, optical coherence tomography (OCT) and a physician assessment. The injection was performed the same day whenever possible. The primary endpoint to evaluate patient adherence was the time between the ideal date of visit or injection prescribed by the physician and the actual date of administration.

RESULTS: The mean time between the ideal date of visit or injection prescribed by the physician and the actual date of administration was 4.1±7.5 days for the patients followed in the fast track and 5.6±18.7 days for the patients followed in the standard protocol. Mean VA remained stable for the patients followed in the fast track: 20/50 (20/800 to 20/20) at baseline vs. 20/50 (20/800 to 20/16) at the conclusion of follow-up. It dropped from 40/50 at baseline to 20/63 at the conclusion of follow-up for the patients followed in the standard protocol.

CONCLUSION: In the context of a fast track, it was possible to improve the adherence of nARMD patients and maintain their VA gain or stabilization achieved after the induction phase.

PMID: 28865938

Surv Ophthalmol. 2017 Sep 4. [Epub ahead of print]

The acute and chronic effects of intravitreal anti-vascular endothelial growth factor injections on intraocular pressure: A Review.

Bracha P, Moore NA, Ciulla TA, WuDunn D, Cantor LB.

Abstract: The acute and chronic effects of repeated intravitreal anti-vascular endothelial growth factor
(VEGF) injections on intraocular pressure (IOP) have not been fully characterized and the development of sustained ocular hypertension could adversely affect patients who are at risk of glaucomatous optic neuropathy. As expected, volume-driven, acute ocular hypertension immediately follows intravitreal injection, but this pressure elevation is generally transient and well-tolerated. Several medications have been investigated to limit acute ocular hypertension following anti-VEGF therapy, but the benefits of pretreatment are not conclusive. Chronic, sustained ocular hypertension, distinct from the short-term acute ocular hypertension following each injection, has also been associated with repeated intravitreal anti-VEGF injections. Risk factors for chronic ocular hypertension include the total number of injections, a greater frequency of injection, and pre-existing glaucoma. Proposed mechanisms for chronic ocular hypertension include microparticle obstruction, toxic or inflammatory effects on trabecular meshwork, as well as alterations in outflow facility by anti-VEGF agents. Although limiting anti-VEGF therapy could minimize the risk of both acute and chronic ocular hypertension, foregoing anti-VEGF therapy risks progression of various macular diseases with resulting permanent central vision loss. While definitive evidence of damage to the retinal nerve fiber layer is lacking, patients receiving repeated injections should be monitored for ocular hypertension and those who subsequently develop sustained ocular hypertension should be periodically monitored for glaucomatous changes with an optic nerve optical coherence tomography (OCT) and static visual fields.

PMID: 28882597

Ranibizumab in Treating Age-Related Macular Degeneration [Internet].

Swedish Council on Health Technology Assessment.


SBU Systematic Review Summaries.

Conclusions: Monthly treatment with ranibizumab has a substantial inhibitory effect on the course of disease compared to photodynamic therapy or sham injection in patients with neovascular age-related macular degeneration – in followup ≤2 years. Monthly treatment improves vision to a substantially higher degree in patients treated with ranibizumab compared to those who received photodynamic therapy or sham injection – in followup ≤2 years. Scientific evidence is insufficient regarding the effects of treatment when delivered less frequently than once per month, or for periods exceeding 2 years. It is unclear whether treatment can be discontinued, or if further treatments are necessary to maintain the effects. Scientific evidence is insufficient to assess the cost-effectiveness of the method.

PMID: 28876727

Other treatment & diagnosis


Plasma metabolomic study in Chinese patients with wet age-related macular degeneration.

Luo D, Deng T, Yuan W, Deng H, Jin M.

BACKGROUND: Age-related macular degeneration (AMD) is a leading disease associated with blindness. It has a high incidence and complex pathogenesis. We aimed to study the metabolomic characteristics in Chinese patients with wet AMD by analyzing the morning plasma of 20 healthy controls and 20 wet AMD patients for metabolic differences.

METHODS: We used ultra-high-pressure liquid chromatography and quadrupole-time-of-flight mass spectrometry for this analysis. The relationship of these differences with AMD pathophysiology was also assessed. Remaining data were normalized using Pareto scaling, and then valid data were handled using
multivariate data analysis with MetaboAnalysis software, including unsupervised principal component analysis and supervised partial least squares-discriminate analysis. The purpose of the present work was to identify significant metabolites for the analyses. Hierarchical clustering was conducted to identify metabolites that differed between the two groups. Significant metabolites were then identified using the established database, and features were mapped on the Kyoto Encyclopedia of Genes and Genomes.

RESULTS: A total of 5443 ion peaks were detected, all of them attributable to the same 10 metabolites. These included some amino acids, isomaltose, hydrocortisone, and biliverdin. The heights of these peaks differed significantly between the two groups. The biosynthesis of amino acids pathways also differed profoundly between patients with wet AMD and controls.

CONCLUSIONS: These findings suggested that metabolic profiles and pathways differed between wet AMD and controls and may provide promising new targets for AMD-directed therapeutics and diagnostics.

PMID: 28874192 PMCID: PMC5585971

Eye (Lond). 2017 Sep 8. [Epub ahead of print]

An overview of the clinical applications of optical coherence tomography angiography.

Tan ACS, Tan GS, Denniston AK, Keane PA, Ang M, Milea D, Chakravarthy U, Cheung CMG.

Abstract: Optical coherence tomography angiography (OCTA) has emerged as a novel, non-invasive imaging modality that allows the detailed study of flow within the vascular structures of the eye. Compared to conventional dye angiography, OCTA can produce more detailed, higher resolution images of the vasculature without the added risk of dye injection. In our review, we discuss the advantages and disadvantages of this new technology in comparison to conventional dye angiography. We provide an overview of the current OCTA technology available, compare the various commercial OCTA machines technical specifications and discuss some future software improvements. An approach to the interpretation of OCTA images by correlating images to other multimodal imaging with attention to identifying potential artefacts will be outlined and may be useful to ophthalmologists, particularly those who are currently still unfamiliar with this new technology. This review is based on a search of peer-reviewed published papers relevant to OCTA according to our current knowledge, up to January 2017, available on the PubMed database. Currently, many of the published studies have focused on OCTA imaging of the retina, in particular, the use of OCTA in the diagnosis and management of common retinal diseases such as age-related macular degeneration and retinal vascular diseases. In addition, we describe clinical applications for OCTA imaging in inflammatory diseases, optic nerve diseases and anterior segment diseases. This review is based on both the current literature and the clinical experience of our individual authors, with an emphasis on the clinical applications of this imaging technology.

PMID: 28885606

Pathogenesis

Life Sci. 2017 Sep 5. [Epub ahead of print]

PPARγ agonists: Potential treatments for exudative age-related macular degeneration.

Vallée A, Lecarpentier Y, Guillévin R, Vallée JN.

Abstract: Choroidal neovascularization (CNV) characterizes the progression of exudative age-related macular degeneration (AMD) with the deterioration in the central vision. Vascular inflammation, and overproduction of inflammatory cytokines, growth factors and aberrant endothelial cell migration, initiate defective blood vessel proliferation in exudative AMD. CNV formation is initiated by the interplay between inflammation, the hallmark of exudative AMD, and the activation of WNT/β-catenin pathway. Upregulation of WNT/β-catenin pathway involves activation of PI3K/Akt pathway and then the Warburg effect to produce
lactate. Lactate production generates VEGF expression and then participates to the initiation of CNV in exudative AMD. WNT/β-catenin pathway and PPARγ act in an opposite manner in several diseases. We focus this review on the interplay between PPARγ and canonical WNT/β-catenin pathway and the anti-inflammatory role of PPARγ in exudative AMD. In exudative AMD, PPARγ agonists downregulate inflammation and the WNT/β-catenin pathway. PPARγ agonists can appear as promising treatment against the initiation and the progression of CNV in exudative AMD.

PMID: 28887057


A Pathogenic Mechanism Potentially Operative in Multiple Progressive Diseases and Its Therapeutic Implications.

Re RN.

Abstract: A variety of peptide signaling moieties that we have termed intracrines can act in the interiors of their cells of synthesis or of target cells after internalization. These intracrine factors are known to be upregulated in such disorders as diabetic nephropathy, systolic heart failure, and age-related macular degeneration. Indeed, a similar set of intracrines is upregulated in each of these disorders, suggesting a commonality of mechanism. In addition, several chronic neurodegenerative disorders such as Alzheimer disease and Parkinson disease involve intercellular trafficking of intracellular disease-causing proteins. These disorders can be considered introcrine-like. Here the mechanistic and therapeutic implications of these observations, and of the relevant modes of introcrine action, are discussed, including the possibility that similar therapeutic approaches could be effective in multiple progressive disorders and the implications of these observations for introcrine pharmacology in general.

PMID: 28884862

Cell Death Dis. 2017 Sep 7;8(9):e3046.

LncRNA ZNF503-AS1 promotes RPE differentiation by downregulating ZNF503 expression.


Abstract: Long noncoding RNAs (lncRNAs) have important roles in various biological processes. Our previous work has revealed that dedifferentiation of retinal pigment epithelium (RPE) cells contributes to the pathology of age-related macular degeneration (AMD). Herein, we show roles of lncRNAs in RPE differentiation. We used microarray to identify lncRNA expression profiles in human induced pluripotent stem cells (hiPSCs) and hiPSC-derived RPE cells. A total of 217 differentially expressed lncRNAs along with the differentiation were initially identified, among which 13 lncRNAs showed a consistent fold change of over 2. LncRNA ZNF503-AS1, located in the cytoplasm of RPE cells, was found consistently upregulated along with RPE differentiation, and downregulated in the RPE-choroid of AMD patients. In vitro study further suggested that ZNF503-AS1 insufficiency could inhibit RPE differentiation, and promote its proliferation and migration. As ZNF503-AS1 is transcribed from the antisense strand of the ZNF503 gene locus, we further revealed its regulatory role in ZNF503 expression. ZNF503-AS1 was reversely correlated with ZNF503 expression. Our results also suggested that ZNF503 could inhibit RPE differentiation, and promote its proliferation and migration. Thus, ZNF503-AS1 potentially promotes RPE differentiation through downregulation of ZNF503 expression. In addition, nuclear factor-κB was recognized as a potential upstream transcript factor for ZNF503-AS1, which might participate in promoting RPE differentiation by regulating the expression of ZNF503-AS1. Taken together, our study identifies a group of RPE differentiation relevant lncRNAs, and the potential role of ZNF503-AS1 in the pathology of atrophic AMD, which might help with the intervention of AMD patients.

PMID: 28880276

Optic Nerve Degeneration after Retinal Ischemia/Reperfusion in a Rodent Model.


Abstract: Retinal ischemia is a common pathomechanism in many ocular disorders such as age-related macular degeneration (AMD), diabetic retinopathy, glaucoma or retinal vascular occlusion. Several studies demonstrated that ischemia/reperfusion (I/R) leads to morphological and functional changes of different retinal cell types. However, little is known about the ischemic effects on the optic nerve. The goal of this study was to evaluate these effects. Ischemia was induced by raising the intraocular pressure (IOP) in one eye of rats to 140 mmHg for 1 h followed by natural reperfusion. After 21 days, histological as well as quantitative real-time PCR (qRT-PCR) analyses of optic nerves were performed. Ischemic optic nerves showed an infiltration of cells and also degeneration with signs of demyelination. Furthermore, a migration and an activation of microglia could be observed histologically as well as on mRNA level. In regard to macroglia, a trend toward gliosis could be noted after ischemia induction by vimentin staining. Additionally, an up-regulation of glial fibrillary acidic protein (GFAP) mRNA was found in ischemic optic nerves. Counting of oligodendrocyte transcription factor 2 positive (Olig2+) cells revealed a decrease of oligodendrocytes in the ischemic group. Also, myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) mRNA expression was down-regulated after induction of I/R. On immunohistological level, a decrease of MOG was detectable in ischemic optic nerves as well. In addition, SMI-32 stained neurofilaments of longitudinal optic nerve sections showed a strong structural damage of the ischemic optic nerves in comparison to controls. Consequently, retinal ischemia impacts optic nerve degeneration. These findings could help to better understand the course of destruction in the optic nerve after an ischemic insult. Especially for therapeutic studies, the optic nerve is important because of its susceptibility to be damaged as a result to retinal ischemic injury and also its connecting function between the eye and the brain. So, future drug screenings should target not only the retina, but also the functionality and structure of the optic nerve. In the future, these results could lead to the development of new therapeutic strategies for treatment of ischemic injury.

PMID: 28878627 PMCID: PMC5572359

Photochem Photobiol. 2017 Sep 5. [Epub ahead of print]

Photodegradation of Eumelanin and Pheomelanin and Its Pathophysiological Implications.

Ito S, Wakamatsu K, Sarna T.

Abstract: Eumelanin is photoprotective for pigmented tissues while pheomelanin is phototoxic. In this review, we summarize current understanding of how eumelanin and pheomelanin structures are modified by ultraviolet A (UVA) and also by visible light and how reactive oxygen species participate in those processes. Alkaline hydrogen peroxide oxidation was employed to characterize eumelanin and benzothiazole-type pheomelanin, giving pyrrole-2,3,5-tricarboxylic acid (PTCA) and thiazole-2,4,5-tricarboxylic acid (TTCA), respectively. Reductive hydrolysis with hydroiodic acid gives 4-amino-3-hydroxyphenylalanine (4-AHP) from the benzothiazine moiety of pheomelanin. The results show that the photoaging of eumelanin gives rise to Free PTCA (produced by peroxidation in situ) and pyrrole-2,3,4,5-tetracarboxylic acid (PTECA, produced by cross-linking). The TTCA/4-AHP ratio increases with photoaging, indicating the conversion of benzothiazine to the benzothiazole moiety. Analysis of those markers and their ratios show that both eumelanin and pheomelanin in human retinal pigment epithelium melanosomes undergo extensive structural modifications due to their life-long exposure to blue light. Using synthetic melamins, we also found that singlet oxygen, in addition to superoxide anions, is photogenerated and quenched upon UVA irradiation. The (patho)physiological significance of those findings is discussed in relation to the tanning process, to melanomagenesis in the skin and to age-related macular degeneration in the eyes. This article is protected by copyright. All rights reserved.

PMID: 28873228
Apln-CreERT:mT/mG reporter mice as a tool for sprouting angiogenesis study.


BACKGROUND: Angiogenesis is defined as a new blood vessel sprouting from pre-existing vessels, and the sprouting angiogenesis is the start phase of angiogenesis, which is critical for both physiological and pathological processes, such as embryonic development, organ growth, wound healing, tumor growth, diabetic retinopathy and age-related macular degeneration. Better understanding of the mechanisms of sprout angiogenesis will provide a rationale for the treatments of these angiogenesis related diseases.

METHODS: mT/mG tool mice are crossed with Apln-CreERT mice to generate Apln-CreERT: mT/mG mice, then we used neonatal retinal angiogenesis model to observe the angiogenic pattern of Apln-CreERT:mT/mG mice compared with Cdh5-CreERT:mT/mG mice. FACS analysis was used to sort eGFP and tdTomato endothelial cells (ECs) for measuring Apelin and Cdh5 expression. Retinal sprouting angiogenesis pattern was also observed at different neonatal time when induced by tamoxifen and at hypoxia condition, as well as in vivo tumor in real-time angiogenesis in a dorsal skinfold window chamber in Apln-CreERT:mT/mG mice.

RESULTS: Apln-CreERT:mT/mG mice exhibited eGFP signal only in the sprouting angiogenesis, with less eGFP expression in the retinal "optic nerve" area than in that of Cdh5-CreERT: mT/mG mice, which might be due to relative mature vessels in the "optic nerve" area. The ECs sorted by FACS confirmed that the Apelin expression level was higher in eGFP ECs than tdTomato ECs of "optic nerve" area. Further we found that GFP-labeled sprouting angiogenesis decreased gradually following tamoxifen administration from P5-P7, but increased significantly during hypoxia in Apln-CreERT:mT/mG mice. At last, using Apln-CreERT:mT/mG mice we found tumor sprouting angiogenesis in dorsal skinfold, but not in the normal skinfold tissue.

CONCLUSIONS: Apln-CreERT:mT/mG mouse line is a useful tool to differentiate sprouting angiogenesis from whole blood vessels in the investigation of retinal and tumor sprouting angiogenesis in vivo.

PMID: 28865439 PMCID: PMC5581477

Epidemiology


Pesticide Use and Age-Related Macular Degeneration in the Agricultural Health Study.

Montgomery MP, Postel E, Umbach DM, Richards M, Watson M, Blair A, Chen H, Sandler DP, Schmidt S, Kamel F.

BACKGROUND: Age-related macular degeneration (AMD) is a leading cause of blindness in developed countries. Few studies have investigated its relationship to environmental neurotoxins. In previous cross-sectional studies, we found an association between pesticide use and self-reported retinal degeneration.

OBJECTIVE: We evaluated the association of pesticide use with physician-confirmed incident AMD.

METHODS: The Agricultural Health Study (AHS) is a prospective cohort of pesticide applicators and their spouses enrolled from 1993-1997 in Iowa and North Carolina. Cohort members reported lifetime use of 50 specific pesticides at enrollment. Self-reports of incident AMD during follow-up through 2007 were confirmed by reports from participants' physicians and by independent evaluation of retinal photographs provided by the physicians. Confirmed cases (n=161) were compared with AHS cohort members without AMD (n=39,108). We estimated odds ratios (ORs) and 95% confidence intervals (CIs) by logistic regression with adjustment for age, gender, and smoking.
RESULTS: AMD was associated with ever use of organochlorine [OR=2.7 (95% CI: 1.8, 4.0)] and organophosphate [OR=2.0 (95% CI: 1.3, 3.0)] insecticides and phenoxyacetate herbicides [OR=1.9 (95% CI: 1.2, 2.8)]. Specific pesticides consistently associated with AMD included chlordane, dichlorodiphenyltrichloroethane (DDT), malathion, and captan; others with notable but slightly less consistent associations were heptachlor, diazinon, phorate, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), and 2,4-dichlorophenoxyacetic acid (2,4-D). Results were similar for men and women. Some specific pesticides were associated with both early- and late-stage AMD, but others were associated with only one stage.

CONCLUSIONS: Exposures to specific pesticides may be modifiable risk factors for AMD.

PMID: 28886597

Genetics & gene therapy

Hum Gene Ther. 2017 Sep 4. [Epub ahead of print]

Wide Awake and Ready to Move: 20 Years of Non-Viral Therapeutic Genome Engineering with the Sleeping Beauty Transposon System.

Hodge R, Narayananvari S, Izsvák Z, Ivics Z.

Abstract: Gene therapies will only become a widespread tool in the clinical treatment of human diseases with the advent of gene transfer vectors that integrate genetic information stably, safely, effectively, and economically. Two decades after the discovery of the Sleeping Beauty (SB) transposon, it has been transformed into a vector system that is fulfilling these requirements. SB may well overcome some of the limitations associated with viral gene transfer vectors and transient non-viral gene delivery approaches that are being used in the majority of ongoing clinical trials. The SB system has achieved a high level of stable gene transfer and sustained transgene expression in multiple primary human somatic cell types, representing crucial steps that may permit its clinical use in the near future. Here we review the most important aspects of SB as a tool for gene therapy, including aspects of its vectorization and genomic integration. As an illustration we highlight clinical development of the SB system towards gene therapy of age-related macular degeneration and cancer immunotherapy.

PMID: 28870121

Stem cells

Proc Natl Acad Sci U S A. 2017 Sep 6. [Epub ahead of print]

Drusen in patient-derived hiPSC-RPE models of macular dystrophies.


Abstract: Age-related macular degeneration (AMD) and related macular dystrophies (MDs) are a major cause of vision loss. However, the mechanisms underlying their progression remain ill-defined. This is partly due to the lack of disease models recapitulating the human pathology. Furthermore, in vivo studies have yielded limited understanding of the role of specific cell types in the eye vs. systemic influences (e.g., serum) on the disease pathology. Here, we use human induced pluripotent stem cell-retinal pigment epithelium (hiPSC-RPE) derived from patients with three dominant MDs, Sorsby's fundus dystrophy (SFD), Doyne honeycomb retinal dystrophy/malattia Leventinese (DHRD), and autosomal dominant radial drusen (ADRD), and demonstrate that dysfunction of RPE cells alone is sufficient for the initiation of sub-RPE lipoproteinaceous deposit (drusen) formation and extracellular matrix (ECM) alteration in these diseases. Consistent with clinical studies, sub-RPE basal deposits were present beneath both control (unaffected) and patient hiPSC-RPE cells. Importantly basal deposits in patient hiPSC-RPE cultures were more
abundant and displayed a lipid- and protein-rich "drusen-like" composition. Furthermore, increased accumulation of COL4 was observed in ECM isolated from control vs. patient hiPSC-RPE cultures. Interestingly, RPE-specific up-regulation in the expression of several complement genes was also seen in patient hiPSC-RPE cultures of all three MDs (SFD, DHRD, and ADRD). Finally, although serum exposure was not necessary for drusen formation, COL4 accumulation in ECM, and complement pathway gene alteration, it impacted the composition of drusen-like deposits in patient hiPSC-RPE cultures. Together, the drusen model(s) of MDs described here provide fundamental insights into the unique biology of maculopathies affecting the RPE-ECM interface.

PMID: 28878022