Kappa opioid receptor antagonism protects working memory performance from mild stress exposure in Rhesus macaques

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ABSTRACT

Extensive preclinical and emerging clinical evidence point to an involvement of the kappa opioid receptor (KOR) in brain networks that promotes neurobehavioral stability. KOR expression in mesolimbic and mesocortical pathways has been the basis for characterizing the role of this receptor system in regulating motivation and emotion; however, the involvement of the KOR system in higher-order executive processes such as working memory (WM) is not well-understood. WM is readily impaired with uncontrollable stress exposure and is dysregulated in many neurobehavioral disorders. To empirically evaluate the role of the KOR system on WM performance, we administered a selective KOR antagonist, NMRA-140 (0, 0.1, 0.3, 1.0 mg/kg, intramuscular) to monkeys under both stress and non-stress conditions. In this study, NMRA-140 was co-administered with FG7142, a benzodiazepine inverse agonist, known to produce a mild stress response and to impair WM function in monkeys. NMRA-140 protected WM performance from the detrimental effects of FG7142-induced stress and exhibited no significant effect under non-stress conditions. Collectively, these data highlight the functional influence of the KOR system in mediating stress-induced dysfunction of executive processes and suggest that modulating KOR activity could offer therapeutic benefit in stress-related neurobehavioral disorders.

1. Introduction

Exposure to uncontrollable stress produces a constellation of behavioral and neurochemical changes, including impaired higher cognitive functions, that are discernible from those caused by controllable stressors and can contribute to and exacerbate neuropsychiatric illness (Maier and Watkins, 2010; Rosch, 1995). The prefrontal cortex (PFC) underlies many of these executive cognitive processes vulnerable to uncontrollable stress conditions through its extensive interconnections both within cortical and amongst subcortical regions. In particular, effective working memory (WM) – the ability to actively maintain and manipulate information ‘online’ during the absence of direct sensory stimulation (Baddeley, 2012) – enables other executive processes such as problem solving and abstract reasoning that are sensitive to dysregulation with stress, aging, and across neuropsychiatric conditions (eg, schizophrenia) (Arnsten et al., 2012). Neurophysiology data collected from individual neurons within the dorsolateral (dl) PFC of nonhuman primates (NHPs) has provided critical insight into WM processes and has defined this region as an essential neural substrate supporting its function (Funahashi et al., 1989; Wang et al., 2013). Human functional neuroimaging data have further corroborated these findings and revealed coordinated activation and deactivation of canonical neuronal network ensembles including fronto-parietal and default mode networks, respectively, which support efficient WM processes (Courtney et al., 1996; Curtis et al., 2004).

Studies in animals and humans have shown that acute, environmental, or pharmacological stress (eg, the anxiogenic beta-carboline FG7142) impairs working memory function through neurochemical changes (Murphy et al., 1996; Shansky et al., 2006), whereas chronic stress causes additional architectural changes in PFC, such as reduced dendritic branching and spine loss in animals, and reduced functional connectivity and gray matter in humans that are associated with impaired cognitive performance (Ansell et al., 2012; Hains et al., 2009; Liston et al., 2009; Shansky et al., 2009). Uncontrollable stress activates the amygdala, and initiates a biochemical cascade of events, including the release of stress-induced neuropeptides and increased monoaminergic neurotransmission (dopaminergic and noradrenergic) within the PFC (Arnsten et al., 2012; Goldstein et al., 1996; Nation et al., 2018). The release of dynorphin neuropeptides activates the kappa opioid receptor antagonism protecting working memory performance from mild stress exposure in Rhesus macaques...
Abbreviations

AUC0-72 area under the concentration-time curve from hour 0 to hour 72, estimated by the linear trapezoidal rule
CeA central nucleus of the amygdala
Cmax maximum observed concentration
dlPFC dorsolateral prefrontal cortex
IC50 half maximal inhibitory concentration
IM intramuscular
KOR kappa opioid receptor
LC locus coeruleus
MOR mu opioid receptor
NHP non-human primate
norBNI nor-binaltorphimine
PFC prefrontal cortex
Tmax time of maximum observed concentration
t1/2 elimination half-life, determined by In(2)/tZ
VTA ventral tegmental area
WM working memory

receptor (KOR) system important in the modulation of emotional and stress circuits (Schwarzer, 2009). In clinical studies, the administration of brain-penetrant KOR agonists elicits dysphoric and depressive symptoms, as well as other psychotomimetic effects (eg, sedation, dizziness, confusion) (Pfeiffer et al., 1986; Walsh et al., 2001). In preclinical studies, activation of KORs with selective agonists results in stress-induced depression- and anxiety-like behaviors and leads to reinstatement of drug seeking in abstinent animals previously dependent on drugs of abuse (Beardsley et al., 2005; Carey et al., 2007; Carlezon et al., 2006; Land et al., 2009). Consistent with these findings, KOR antagonists reduce stress behaviors in in vivo animal models (Mague et al., 2003; Newton et al., 2002; Pliakas et al., 2001). Moreover, rats exposed to uncontrollable stressors such as immobilization or inescapable stress show increased dynorphin protein concentrations in limbic brain regions such as hippocampal fields and nucleus accumbens, further implicating the KOR system in stress responses (Shirayama et al., 2004).

KORs are widely expressed throughout the brain and are enriched in mesolimbic and mesocortical circuits, supporting their role in stress-induced alterations in reward and emotional processing (Chavkin et al., 1982; Mague et al., 2003; Van’t Veer and Carlezon, 2013). Despite their localization in cortical brain regions, less is known about the involvement of the KOR system in executive processes, including WM. A study in rodents recently showed infusions of a KOR agonist into the medial PFC caused impairments in a delayed WM task that could be prevented by the pretreatment of a KOR antagonist, providing support for KOR involvement in PFC-mediated cognitive processing (Wei et al., 2022).

The intent of the present study was to evaluate the involvement of the KOR system in working memory function in nonhuman primates. Recently, the potent and selective small molecule KOR antagonist NMRA-140 (also known as BTRX-335140) was described to exhibit ideal pharmacokinetic properties, including a duration of action in rat pharmacodynamic experiments consistent with a potential medication (Guerrero et al., 2019). We tested whether modulation of the KOR system through systemic administration of NMRA-140 impacted WM performance in Rhesus macaques under both nonstress and mild stress conditions.

To evaluate NHP behavior under mild stress conditions, we used FG7142, a partial inverse agonist that acts allosterically at the benzodiazepine site of the GABA<sub>A</sub> receptor. FG7142 is a well-characterized pharmacological stressor demonstrated to produce anxiogenic responses in rodents, NHPs, and healthy human volunteers, including elevated cortisol release; these responses can be reversed by benzodiazepine administration (Dorow et al., 1983; Evans and Lowry, 2007; Major et al., 2009; Stout and Weiss, 1994; Takamatsu et al., 2003; Takeda et al., 1998). In preclinical studies, administration of FG7142 results in both behavioral and physiological stress responses, including increased stress-related behaviors, increased plasma cortisol levels, and decreased cerebral blood flow (Evans and Lowry, 2007; Takamatsu et al., 2003). The effects of FG7142 have been shown to be identical to an environmental stressor, loud (>95 dB) white noise (Arnst and Goldman-Rakic, 1998; Murphy et al., 1996). FG7142 has also been demonstrated to induce cognitive deficits and hinder the completion of WM tasks in both rodents and NHPs (Arnst et al., 2000; Birnbaum et al., 2000).

2. Materials and methods

2.1. In vitro functional assays

NMRA-140 was assessed for antagonist properties using Tango™ assay technology (Zlokarnik et al., 1998) in recombinant U2OS cell lines stably expressing the OPRK1 (KOR) or OPRD (DOR) genes. In these cells, NMRA-140 (HCl salt form) was assessed in triplicate during 3 separate test sessions in response to challenge with the KOR synthetic agonist U-50,488 (3.5 nM; Sigma Aldrich, St. Louis, MO) or the DOR agonist SNC80 (175 nM; Sigma Aldrich, St. Louis, MO).

Functional antagonism of the MOR was assessed in the PathHunter® β-arrrestin cell lines (DiscoverX, Fremont CA) stably expressing the OPRM1 gene; well luminescence was measured using a GPCR-β-arrrestin proximity assay. NMRA-140 was assessed in triplicate on 3 separate test sessions for antagonist properties at the MOR using the MOR agonist DAMGO (250 nM; Sigma Aldrich, St. Louis, MO). Data are expressed as mean ± SEM.

2.2. Animals

Adult Rhesus macaques (n = 6; 2 male and 4 female, 12–27 years old at the end of the study) were maintained under constant environmental conditions (temperature 21 ± 3 °C; humidity 30–70%; 12:12 h light: dark cycle with lights on at 06:00 and off at 18:00). All animals received a full daily regimen of standard certified commercial chow (Purina Animal Nutrition, Gray Summit, MO) supplemented with fresh fruit and vegetables after testing each day and had access to water ad libitum in their home cage. Animals were pair-housed and had planned environmental enrichment during the day. The research was approved by the Yale Animal Care and Use Committee.

During the study, monkeys were tested by an experimenter who was very familiar with the normative behavior of that animal but was blind to drug treatment conditions and had no knowledge regarding the hypothesis under investigation. Monkeys were selected for inclusion in the study based on stable performance and were rated for changes in sedation, agitation, aggression, pallor, and any unusual behaviors, in addition to accuracy of task performance and trial completion. There was at least a 10-day washout period between drug treatments.

2.3. In vivo pharmacokinetics

Rhesus macaques (n = 2; young adult male, non-naïve) were administered intramuscular (IM) NMRA-140 at 0.06, 0.3 and 1.0 mg/kg. Blood was collected via femoral vein at 0.5, 1, 2, 4, 8, 24, 48, and 72 h after administration and transferred into chilled tubes containing K<sub>3</sub>EDTA prior to centrifugation to obtain plasma. Samples were analyzed for concentrations of NMRA-140 using an established liquid chromatography/mass spectrometry method.
2.4. Delayed response working memory task

Monkeys had been pretrained on the classic, manual version of the delayed response test of spatial working memory in a Wisconsin General Testing Apparatus (WGTA; Arnsten and Goldman-Rakic, 1998). Briefly, the delayed response working memory task consists of baiting one of two food wells in full view of the animal, then covering the food wells for a prespecified amount of time prior to allowing the animal to choose between wells. Five different delay lengths (i.e., 0, 5, 10, 15, and 20 s) quasi-randomly distributed over 30 trials were used in each session to assess drug effects on the range of working memory capabilities; delays were adjusted so that each animal had a stable baseline performance of 60%-80% correct, thus providing room for either impairment or improvement in task performance with drug treatment. It has been shown previously that stress impairs performance of this working memory task without altering visual pattern recognition or motivation (Arnsten and Goldman-Rakic, 1998; Arnsten et al., 2000). Monkeys were required to complete all the trials in a session and return to stable baseline performance for 2 consecutive sessions prior to receiving drug administration; thus, washout periods were at least 10 days between doses. Performance accuracy was calculated as trials correct/total trials x 100%.

2.5. Treatments administered

In the non-stress condition, Rhesus macaques (n = 6) were given IM injections of NMRA-140 (0, 0.1, 0.3, 1.0) 30 min prior to testing. NMRA-140 was dissolved in a vehicle containing N-methyl-2-pyrrolidinone/PEG 400/18% Tween 80 in water/60% Cremophor EL in Propylene Glycol/20 mL Na2HPO4 (pH 9-10) in sterile water. In the stress condition, NMRA-140 was co-administered with the inverse benzodiazepine partial agonist FG7142. FG7142 was made fresh daily by dissolving it in 0.2 mL 100% ethanol and 0.8 mL 2-hydroxylpropyl-β-cyclodextrin (HBC) vehicle/kg, followed by sonication. The HBC vehicle was made by dissolving 1.5 mg HBC (Sigma-Aldrich, St. Louis, MO) in 1 mL Tween 80 (Sigma-Aldrich) and 7.4 mL sterile saline overnight. Doses of NMRA-140 were selected based on pharmacokinetic properties of the compound and were calculated to have KOR occupancies >60% which is estimated to be sufficient for efficacy (Grimwood and Hartig, 2009; Rorick-Kehn et al., 2014).

FG7142 was administered IM 30 min before testing. Doses of FG7412 were individually titrated for each monkey to sufficiently impair task accuracy without compromising the ability of the animal to conduct the task by inducing unwanted behaviors such as aggression, agitation, or withdrawal from performing the task. Five of 6 monkeys demonstrated reliable impairment with FG7142 treatment and were used to assess the effects of NMRA-140 on the stress response. Specifically, the impairing doses of FG7142 identified and administered to the five monkeys in this study were 0.1, 0.3, 0.5, 0.7 and 1.0 mg/kg.

2.6. Statistical analysis

NHP WM data were analyzed using a one-way repeated measures analysis of variance with Geisser-Greenhouse correction for sphericity followed by Dunnett’s post hoc analysis (GraphPad Prism v8, San Diego, CA). Significance was defined as P < 0.05.

3. Results

3.1 NMRA-140 pharmacology. NMRA-140 was characterized in in vitro recombinant systems stably expressing the human OPRK1 (KOR), OPRM1 (MOR), and OPRD (DOR) genes. The compound demonstrated subnanomolar potency (half maximal inhibitory concentration [IC50] = 0.8 nM) at KOR (Guerrero et al., 2019; Table 1). In comparison to the closely related mu and delta opioid receptor targets, NMRA-140 was 138-fold more potent at the KOR than at the MOR (IC50 = 110 nM), and >-8000-fold more selective at the KOR than at the DOR (IC50 = 6500 nM).

For the purposes of this study, we considered the potency of NMRA-140 at the macaque KOR to be consistent with data we collected from the human KOR. The OPRK1 gene is highly conserved across higher and lower species. The human and macaque share OPRK1 sequence alignment of 92.6% at the protein level and 93.5% at the DNA level.

3.2 NMRA-140 pharmacokinetics (PK) in Rhesus macaques. A single-dose PK study with NMRA-140 (0.06, 0.3, 1.0 mg/kg) was conducted to aid in dose selection and pretreatment times in preparation for the WM assessment in macaques. After intramuscular administration, NMRA-140 was absorbed, with mean time of maximum observed concentration (Tmax) values ranging from 0.5 to 1.0 h. After reaching maximum observed concentration (Cmax), NMRA-140 concentrations declined, with the mean elimination half-life, determined by ln(2)/λz, values ranging from 1.9 to 2.4 h (Fig. 1). Overall, exposure to NMRA-140 increased with dose level from 0.06 to 1 mg/kg. The increase in NMRA-140 mean, Cmax, and AUC(0–24h) values was less than dose proportional (Table 2).

3.3 NMRA-140 effects on working memory under control vs stress conditions. In an initial study, we evaluated NMRA-140 (0.1, 0.3, and 1.0 mg/kg) on its own for potential side effects and/or effects on WM in Rhesus macaques that had been trained to stable baseline performance (~20/30 trials correct/session) on the delayed-response WM task. Performance was compared to vehicle control. NMRA-140 had no effect on WM performance (F(2,6, 13) = 1.7; P = 0.21; Fig. 2a), no change in omissions (uncompleted trials) and no apparent side effects. Thus, these doses were deemed appropriate for challenge of the stress response. In a separate study, monkeys were co-administered NMRA-140 (0, 0.1, 0.3, 1.0 mg/kg) with the pharmacological stressor FG7142 and compared to vehicle control (vehicle + vehicle, vehicle + FG7142, NMRA-140 + FG7142 - for each of the 3 NMRA-140 doses). The administration of FG7142 with vehicle produced the expected reduction

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### Table 1

| NMRA-140 in vitro potency |  |
|---------------------------|--|
| Assay                     | IC50 |
| KOR ([−] U50488 agonist)  | 0.8 nM |
| MOR (DAMGO agonist)       | 110 nM |
| DOR (SNC80 agonist)       | 6500 nM |

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Fig. 1. Mean plasma concentrations of NMRA-140 following single administration in Rhesus macaques. NMRA-140 (0.06, 0.3, and 1 mg/kg, intramuscular) was administered to male macaques (n = 2) and 8 blood samples were collected between 0.5 and 72 h.
in performance accuracy to approximately chance levels (54%, Fig. 2b), without increasing omissions. In contrast, co-administration of any of the 3 doses of NMRA-140 (0.1, 0.3, or 1.0 mg/kg) with FG7142 blocked the detrimental effects of FG7142 on cognitive accuracy, with monkeys performing at levels similar to vehicle + vehicle control. A significant main effect of treatment was observed in this study ($F_{(1,6, 6.5)} = 8.8; p = 0.02$). Post hoc analyses revealed significant differences between vehicle + vehicle and FG7142 + vehicle treatments, and between FG7142 + vehicle and FG7142 + NMRA-140 (0.1, 0.3, and 1.0 mg/kg) treatments ($all P < 0.05$). No significant differences were noted between vehicle + vehicle and FG7142 + NMRA-140 treatments. Thus, all 3 doses of NMRA-140 were able to block the cognitive-impairing effects of FG7142 on working memory.

4. Discussion

In this study, we explored the involvement of the KOR system on WM function. Our results in the monkey provide experimental evidence for the involvement of the KOR system in this executive process and suggest that KOR activation is necessary to produce stress-induced impairments in WM performance.

The KOR system regulates negative emotional states with data from both human and animal studies confirming that KOR activation produces aversive dysphoric-like effects (Carlezon et al., 2006; Land et al., 2009; Peiﬁer et al., 1986; Walsh et al., 2001). Moreover, upregulation of dynorphins generates aversive states during withdrawal or abstinence from addictive substances (Koob, 2003; Koob and Volkow, 2010; Shippenberg et al., 2007). Thus, it has been hypothesized that both the aversive responses to stress and dysphoric-like responses during withdrawal from drugs of abuse are mediated by an increase in dynorphin’s actions. Less well-explored is the impact the KOR system may have in mediating executive processes. Although dynorphin mRNA and protein are expressed in the dIPFC, this peptide system previously has been postulated to play a role in executive function eg, cognitive control of addiction (Bazov et al., 2013). KORs in the medial PFC have been shown to negatively regulate dopamine and amino-acid neurotransmission necessary for KOR-mediated conditioned place aversion (Tejeda et al., 2013), thereby establishing precedence for the KOR system acting in PFC regions to effect function.

The PFC regulates catecholamine inputs through its direct and indirect connections to and from monoamine cell bodies in the brainstem (eg, locus coeruleus [LC] and ventral tegmental area [VTA]), and optimal levels of catecholamine release are needed for WM performance (Arnston et al., 2012). However, under conditions of mild environmental or pharmacological stress, there is increased catecholamine release and turnover in the PFC (Deutch and Roth, 1990; Herman et al., 1982; Roth et al., 1988; Thierry et al., 1976), associated with impaired spatial working memory accuracy (Murphy et al., 1996). As it has been shown previously, the anxiogenic compound, FG7142, significantly impairs WM performance in rats and monkeys (Murphy et al., 1996), and similarly increases catecholamine release in the PFC (Birnbaum et al., 1999; Bradberry et al., 1991; Deutch and Roth, 1990; Murphy et al., 1996; Nakane et al., 1994; Tam and Roth, 1985). Consistently, FG7142 reduced performance accuracy in the monkeys in the present study to approximately chance levels without impairing their ability to perform the task. NMRA-140 at all doses tested prevented the WM impairment caused by FG7142, suggesting that by antagonizing dynorphin’s aversive action at KORs NMRA-140 is acting downstream of the FG7142 stress-induced response. In addition, NMRA-140 may be modulating catecholamine levels to more optimal concentrations to preclude the impairing effects of FG7142 administration on WM function.

Although the regional site(s) of action for NMRA-140’s effects on
stress-induced WM in the brain remains to be determined, the amygdala is recognized as an important modulator in the coordination of behavioral, neuroendocrine, and prefrontal cortical monoamine responses to psychological stress (Goldstein et al., 1996). In particular, the central nucleus of the amygdala (CeA) contains dynorphin and other stress-related neuropeptides (eg, corticotropin releasing factor; Koob, 2017), and neuroanatomical tract tracing studies have demonstrated that the CeA projects to the VTA and LC, among other areas (Gonzales and Chesselet, 1996; Wallace et al., 1989, 1992). Under conditions of stress, increased dynorphin release leads to a decrease in GABAergic neurotransmission in the amygdala (Koob, 2017) and results in an excitation of neurons within downstream projection targets, such as the LC and VTA (Lammel et al., 2011; Reyes et al., 2011; Van Boekelstael et al., 1998). Overactivation of catecholamine neurons increases norepinephrine and dopamine release in the PFC region and impairs WM function (Arnsen et al., 2012). These data suggest the CeA may be a locus for the integration of emotional and cognitive responses to stress for which NMRA-140 may act to reduce stress-induced WM deficits by blocking dynorphin’s actions on KORs.

NMRA-140 may also act to interfere with KOR signaling at other neural substrates including the PFC itself. Tejeda et al. (2015) have demonstrated that stress-induced activation of basolateral amygdala projections into mPFC is regulated by KORs and increases anxiety-like behaviors in rodents. In addition, Wei et al. have demonstrated that intra-mPFC infusion of a KOR agonist (U-50,488) impaired WM performance in the rat and pretreatment with nor-BNI ameliorated these deficits (Wei et al., 2022). At present, it is not clear how these findings would extend to influence WM function within primate species in which diPFC mechanisms may also contribute to the response, but they do provide additional support for the involvement of the KOR system in stress-induced behaviors.

Although NMRA-140 prevented WM impairment under conditions of mild stress, it neither improved nor impaired WM performance when administered in the absence of FG7142, likely reflecting low baseline mild stress, it neither improved nor impaired WM performance when dose and had a short Twashout period between doses. NMRA-140 was rapidly absorbed and stress-induced behaviors. dlPFC mechanisms may also contribute to the response, but they do provide additional support for the involvement of the KOR system in stress-induced behaviors. Although NMRA-140 prevented WM impairment under conditions of mild stress, it neither improved nor impaired WM performance when administered in the absence of FG7142, likely reflecting low baseline dynorphin concentrations in the brain under nonstress conditions. A administered in the absence of FG7142, likely reflecting low baseline mild stress, it neither improved nor impaired WM performance when dose and had a short Twashout period between doses. NMRA-140 was rapidly absorbed and stress-induced behaviors. dlPFC mechanisms may also contribute to the response, but they do provide additional support for the involvement of the KOR system in stress-induced behaviors. NMRA-140 may also act to interfere with KOR signaling at other neural substrates including the PFC itself. Tejeda et al. (2015) have demonstrated that stress-induced activation of basolateral amygdala projections into mPFC is regulated by KORs and increases anxiety-like behaviors in rodents. In addition, Wei et al. have demonstrated that intra-mPFC infusion of a KOR agonist (U-50,488) impaired WM performance in the rat and pretreatment with nor-BNI ameliorated these deficits (Wei et al., 2022). At present, it is not clear how these findings would extend to influence WM function within primate species in which diPFC mechanisms may also contribute to the response, but they do provide additional support for the involvement of the KOR system in stress-induced behaviors.

Collectively, our results suggest that in the presence of a mild stressor (FG-7142), NMRA-140 fully prevented the working memory impairment and maintained performance equivalent to the vehicle condition in NHPs, with no impact on performance when tested on its own. The data from the present study, combined with a vast literature demonstrating a role for KOR in reward processing, suggest that the KOR system is positioned at the intersection of the motivational and executive function circuits, which may have therapeutic benefit for neurobehavioral disorders.

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CRediT authorship contribution statement

Tanya L. Wallace: Conceptualization, Formal analysis, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. William J. Martin: Conceptualization, Formal analysis, Funding acquisition, Visualization, Writing – original draft, Writing – review & editing. Amy F.T. Arnsen: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: T. L. Wallace is an employee of Neumora Therapeutics, Inc. (which acquired BlackThorn Therapeutics, Inc.) and has ownership interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds) in Neumora Therapeutics, Inc.; W.J. Martin, a former employee of BlackThorn Therapeutics, Inc.; holds an ownership interest (stock) in Neumora Therapeutics, Inc. as a result of the acquisition of BlackThorn Therapeutics, Inc. by Neumora Therapeutics, Inc. in November 2020; A.F.T. Arnsen had a Contracted Research/Research Grant with BlackThorn Therapeutics. A. F.T.A and Yale receive royalties from the USA sales of Intuniv (non-generic) from Shire/Takeda Pharma.

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